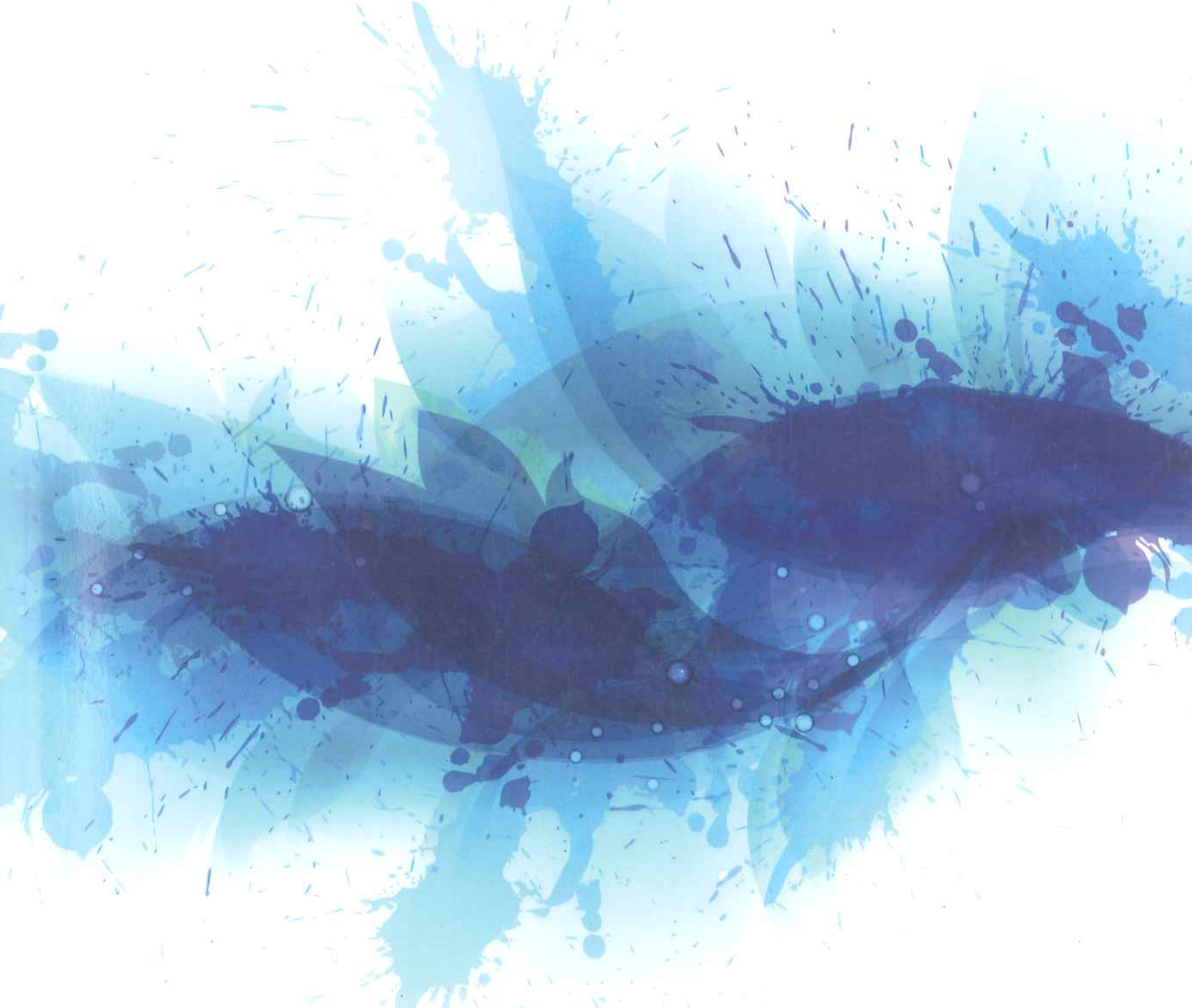
UROLOGY IN-SERVICE AND BOARD REVIEW

THE ESSENTIAL AND CONCISE STUDY GUIDE



JASON D. FISHER

WITH CONTRIBUTING AUTHORSHIP BY **TAREK PACHA**

FORWARD BY **RICHARD A. SANTUCCI**

AN IMPORTANT NOTICE TO OUR READERS

This book should only be utilized by trained healthcare professional with advanced training in the covered topics. This book is not a substitute for qualified medical education and training.

The authors worked diligently and meticulously to insure that Urology In-Service and Board Review - The Essential and Concise Study Guide provides accurate and up-to-date (at the time of its writing) information. The authors relied heavily on other, presumably reliable and valid scientific works, such as medical textbooks, journal articles, and websites, for much of the information provided in this book. Typographical errors, printer errors, inaccuracies, or omission of important material may exist in this book. Moreover, ongoing and future research may render material obsolete in this book. These and other unforeseen factors contribute to the possibility that this book contains inaccurate, erroneous, and obsolete information. Readers should independently verify all information prior to its use or implementation in clinical practice.

This book provides summarized guidelines for the diagnosis and treatment for numerous medical ailments. The authors did not include every possible diagnosis, treatment, or method(s) to arrive at the best possible diagnosis or treatment. Moreover, this book is a study guide and, as such, does not provide comprehensive information about diagnosis and treatment. Readers should independently determine the best diagnostic and treatment options for their unique patient's circumstances, and should never rely solely on this study guide.

The Food and Drug Administration (FDA) may not have approved all medications and medical devices for indications listed in this study guide. Readers should independently verify the FDA's approved use for each medication and medical device, as well as investigate and follow specific FDA guidelines as it relates to each medication and medical device.

The information contained in this study guide is subject to change at any time.

This study guide is published with no expressed or implied warranties or guarantees. No expressed or implied warranties or guarantees are made that the information contained in this book will lead to a passing score on the in-service and board review examinations.

The authors, publisher, and all others involved in the production of this book disavow all liability, injuries, losses, expenses, harms, and any unforeseen consequences from the use or misuse of this study guide or the implementation of material in this study guide.

The reader agrees to all terms above. If the reader is not in agreement with the above terms, they are encouraged to seek out other medical reference books.

TABLE OF CONTENTS

For more information about this book: ii
An Important Notice To Our Readers iv
Forward ix
Tables and Figures x
Abbreviations. xvii
Introduction xxi
Chapter 1: Embryology 1
Chapter 2: Anatomy 12
Chapter 3: Urogenital Anomalies. 34
Chapter 4: Urologic Radiology. 50
Chapter 5: Adrenal Tumors. 72
Chapter 6: Renal Tumors 85
Chapter 7: Renal Pelvis and Ureteral Tumors. 104
Chapter 8: Bladder Tumors 107
Chapter 9: Prostate Cancer 128
Chapter 10: Urethral Tumors 153
Chapter 11: Penile Tumors 156
Chapter 12: Testicular Tumors. 165
Chapter 13: Primary Retroperitoneal Tumors. 183
Chapter 14: Pediatric Tumors. 186
Chapter 15: Pediatric Urology 194
Chapter 16: Bladder Physiology and Neurogenic Bladder 215
Chapter 17: Bladder Dysfunction and Urinary Tract Fistulas 230
Chapter 18: Urinary Dynamic Studies (UDS) 247
Chapter 19: Benign Prostatic Hyperplasia (BPH). 255

Chapter 20: IC / Prostatitis / CPPS. 267
Chapter 21: Urinary Tract Calculi. 273
Chapter 22: Urethral Disease 290
Chapter 23: Upper Urinary Tract Trauma 300
Chapter 24: Lower Genitourinary Trauma. 309
Chapter 25: Sexual Dysfunction 322
Chapter 26: Infertility. 342
Chapter 27: Intersexuality / DSD 362
Chapter 28: Sexually Transmitted Diseases 375
Chapter 29: Infections. 387
Chapter 30: Hydronephrosis 407
Chapter 31: Nephrology 415
Chapter 32: Renovascular Hypertension 434
Chapter 33: Renal Transplant. 442
Chapter 34: Surgery 459
Chapter 35: Syndromes 469
References 479

FORWARD

There are dozens of "compact" general urology overview books. While they do a great job of covering the totality of clinical urology, they can be suboptimal for directed review of your upcoming urology Boards or In-service exams. This book is different. It's designed to be THE overview source for your urology Board/In-service studying. Let's agree that to be a successful urologist, you have to painstakingly study and learn the totality of the urology opus. But, after you spend 11 of 12 months every year learning and reviewing this huge quantity of material (Campbell's Urology runs some 3945 pages), it can be very useful to spend the last month before your big exam reviewing a compact, directed summary of all that material. Here is that summary.

The book is written with the "review study" task in mind. It is brief and bulleted. Complex issues are simplified with algorithms. Explanations for difficult topics are included, but with minimal added clutter. Its topics have been closely correlated to the last 5 years of SASP Urology In-service Review questions to make sure that it covers what you need for your exams. I could go on....

This book is written by two urologists with special qualification. They are near-professional "testologists." Both have achieved perfect and near-perfect scores respectively on their In-service. Both sought the ideal text for their In-service studying, and found none in print that met their high expectations. They completed this project as a labor of love and perhaps out of sheer cussedness: they are the type of people who, when they find the world doesn't have a resource they are sure it needs, they create it.

Enjoy it. And good luck on your test.....

Richard A. Santucci, MD, FACS
Specialist-in-Chief, Urology, The Detroit Medical Center
Clinical Professor, Michigan State College of Osteopathic Medicine

TABLES AND FIGURES

Chapter 1
Indifferent Gonad Genetic Influence (Figure)
Male Hormonal Development
Summary Of Embryologic Structures And Vestigial Remnants

Chapter 2
Rectus Sheath (Anterior Abdominal Wall)
Pituitary Gland
Nerve Origin And Function
Testicular Vasculature / Innervation
Scrotal Layers And Associated Contributions
Quick Reference Table For Arterial Supply

Chapter 3
Calyceal Diverticulum Treatment
Urachal Anomaly Description

Chapter 4
Ct Scan Hounsfield Units
Mag3 Half-Life Interpretation
Vesicoureteral Reflux Grading
Bosniak Scale And Management
Varicocele Grading

Chapter 5

Adrenal Incidentaloma Malignancy
Cushing's Syndrome Workup Algorithm (Figure)
Functional Adenoma Lab Testing Summary

Chapter 6

Representation Of Renal Cell Carcinoma Types
Hereditary Tumor Findings
AUA RCC Follow-Up Guidelines

Chapter 8

Bladder Cancer PLND Templates
High Risk NMIBC Cystectomy Timing And Survival
Bladder Cancer Surveillance
Summary Of Metabolic Disturbances With Conduits

Chapter 9

Reference Ranges Of Age & Race Related PSA (Ng/Ml)
AUA PSA Recommendations
Percentage Of Prostate Cancer Per Zone
PSA And Risk Of Metastasis
D'amico Prostate Cancer Risk Categories
Tumor Extension Affect On Post-Prostatectomy PSA-Free Survival
Primary XRT With Concurrent ADT: Based On Risk Group
CRPC Medication Summary
Adenocarcinoma Vs. Small Cell / Anaplastic Subtype
Prostate Cancer Algorithm (Figure)

Chapter 10

Male Urethral Carcinoma Summary
Female Urethral Carcinoma Summary

Chapter 11
Summary Of Inguinal Lymph Node Dissection Templates

Chapter 12
Testicular Cancer Types (Figure)
Cryptorchidism Treatment Based On Age And Health Status
Summary Of Testicular Cancer Tumor Markers
Testicular Tumor Marker Risk Categories
Testicular Cancer Risk Categories
Pet Scan Statistics
RPLND Templates
Seminoma Treatment Algorithm (Figure)
Nonseminoma Treatment Algorithm (Figure)

Chapter 14
Wilms Tumor Staging (Based On Surgery)
Neuroblastoma Staging/Treatment
Age Of Presentation Summary For Pediatric Tumors

Chapter 15
Defining Antenatal Hydronephrosis
Postnatal Management Of Antenatal Hydronephrosis
SFU Infant (Postnatal) Hydronephrosis
VUR Grading On VCUG
Approximate Spontaneous VUR Resolution Rates
Hypospadias Location
Cryptorchidism Treatment

Chapter 16
Summary Of Urodynamic Findings In CNS Lesions
Parkinson's Vs. Shy Drager Neurogenic Bladder
Summary Of Neurologic Testing

Chapter 17
Incontinence And Pregnancy
Pelvic Organ Prolapse Quantification
POP-Q Measurements
Interpositional Flaps For Fistula Repairs

Chapter 18
Uroflowmetry Diagnostic Findings
Uroflow Maximum Flow Rate Normal Ranges
Qmax / Pdet Obstruction Nomogram (Figure)
VLPP Pressures, Diagnosis, And Treatment
Detrusor Contractility
Cystometrogram Summary

Chapter 19
Uroflow Maximum Flow Rate
Bladder Changes Secondary To BPH

Chapter 20
Prostatitis Classification
Chronic Pelvic Pain Syndrome UPOINT Classification

Chapter 21
Calculi Promoters And Inhibitors
Hypercalciuria Lab Findings
Summary Of Urinary Calculi Findings
Urinary Calculi Microscopy (Figure)
Diseases Associated With Renal Calculi

Chapter 22
Urethral Stricture Treatment Summary

Chapter 24
Bladder Injury Summary
Urethral Blunt Trauma Classification

Chapter 25
Most Common Etiologies Of Priapism
Priapism Presenting Symptoms Comparison
Cavernous Blood Gas Findings

Chapter 26
Semen Composition
Varicocele Grading
Semen Analysis Characteristics
Azoospermia: Obstructive Vs. Non-Obstructive
Summary Of Serum Infertility Findings
Summary Of Semen Analysis And Possible Diagnoses

Chapter 27
Steroid Pathway (Figure)
Summary Of Disorders Of Androgen Synthesis / CAH

Chapter 28
Summary Of Syphilis
Ulcerative STD Summary
HIV CD4 Count-Associated Infections

Chapter 29
Schistosomiasis Presentation
Genitourinary Tb Image Findings
Antibiotic Summary

Chapter 30

Acute Pathophysiology Of Ureteral Obstruction
Antenatal Hydronephrosis Grading
Mag3 Half-Life Interpretation
Whitaker Test Interpretation
Vesicoureteral Reflux Grading

Chapter 31

Electrolyte Absorption Within The Nephron
Tumor Lysis Syndrome Metabolic Abnormalities
Summary Of Lab Findings In Pre-Renal Aki Versus ATN
Chronic Renal Disease Classification
Acid / Base Summary

Chapter 32

Goldblatt Kidney Model
Summary Of Fibromuscular Dysplasia
Surgical Revascularization Success Rates

Chapter 33

ABO Blood Group Compatibility
Immune System Activation And Immunosuppressants (Figure)

Chapter 34

Coagulation Cascade

ABBREVIATIONS

ACTH = adrenocorticotropic hormone
ADH = antidiuretic hormone (vasopressin)
AFP = alpha-fetoprotein
AJCC = American Joint Committee on Cancer
AKI = acute kidney injury
AML = angiomyolipoma
ATN = acute tubular necrosis
β-hCG = beta-human chorionic gonadotropin
BCG = Bacillus Calmette–Guérin
BID = twice daily
BPH = benign prostatic hypertrophy
CaP = prostate cancer
CaT = testicular cancer
Chromo = chromosome
CKD = chronic kidney disease
Cl = chloride
Cr = creatinine
CIC = clean intermittent catheterization
CRH = corticotropin-releasing hormone
CT = computed tomography
Dx = diagnosis
DDx = differential diagnosis
DVC = dorsal venous complex
EMG = electromyography
ESRD = end stage renal disease

ESWL = extracorporeal shockwave lithotripsy
ETOH = alcohol
FISH = fluorescence in situ hybridization
FSH = follicle stimulating hormone
GAG = glycosaminoglycan
GCT = germ cell tumor
GFR = glomerular filtration rate
H&E = hematoxylin and eosin stain
HCO3 = bicarbonate
HTN = hypertension
HU = Hounsfield units
IMA = inferior mesenteric artery
IPSS = international prostate symptom score
IV = intravenous
IVC = inferior vena cava
K = potassium
KUB = kidney ureter bladder x-ray
LDH = lactate dehydrogenase
LH = luteinizing hormone
MC = most common
Met(s) = metastasis
MIS = Mullerian inhibitory substance
Na = sodium
NAAT = nucleic acid amplification test
NNT = number needed to treat
NPV = negative predictive value
OAB = overactive bladder
PCNL = percutaneous nephrolithotomy
pCO2 = partial pressure of carbon dioxide
PFS = progression free survival
PLND = pelvic lymph node dissection
POMC = pro-opiomelanocortin
PPV = positive predictive value

PRN = as needed
PSAG = post-streptococcal acute glomerulonephritis
PTH = parathyroid hormone
QID = four times per day
RAAS = renin angiotensin aldosterone system
RBC = red blood cell
RCC = renal cell carcinoma
RPGN = rapidly progressive glomerulonephritis
RPLND = retroperitoneal lymph node dissection
RR = relative risk
RTA = renal tubular acidosis
SCC = small cell carcinoma
SE = side effects
SMA = superior mesenteric artery
SqCC = squamous cell carcinoma
STD = sexually transmitted disease
TB = tuberculosis
TCC = transitional cell carcinoma
TID = three times daily
TOT = transobturator tape (sling)
TRT = testosterone replacement therapy
TUMT = transurethral microwave therapy
TURBT = transurethral resection of bladder tumor
TURP = transurethral resection of prostate
Tx = treatment
UDT = undescended testicles
UTI = urinary tract infection
VCUG = voiding cystourethrogram
VEGF = vascular endothelial growth factor
VHL = von Hippel Lindau
VUR = vesicoureteral reflux
XRT = external beam radiation therapy

INTRODUCTION

This book is designed to help improve urology residents' in-service scores and to provide a concise review for busy urologists who plan to take the board examinations. The authors expertly condense the essential urological concepts into a single, reliable reference source. Every aspect of this study guide was designed to achieve rapid results in the shortest amount of time. Most material is presented in a bullet point format so that the reader can gather high-yield information without being bogged down by minutiae. Bold and italicized text draws attention to important topics, while "High-Yield Boxes" highlight vital information. 100+ tables and figures condense complex information to improve memory recall during actual testing situations. Complex disease treatment algorithms, such as testicular and prostate cancer, are included.

The authors would like to provide a few suggestions to further improve your test score. First, readers should review the *Syndromes* chapter (i.e., Chapter 35) just prior to the exam as many of these diseases may appear as distractor answer choices. During these high-stakes examinations, the quick elimination of the wrong answer choices will increase your odds of achieving a higher score. In addition, the reader is highly encouraged to utilize the excellent pathology slide review on the AUA website (www.auanet.org) in conjunction with this book. At a minimum, review the slides of the most common tumors for renal, bladder, prostate, and testicular. The pathology slides are highly relevant to the examinations and may appear on your test.

The authors look forward to your feedback (www.bmedpress.com/contact). They plan to provide an up-to-date, concise review of Urologic Surgery for residents and attendings in upcoming editions.

CHAPTER 1: EMBRYOLOGY

The urogenital system develops from intermediate mesoderm

| ADRENAL GLAND |

- Starts forming during the 6th week
- Cortex = ***mesoderm***
    - At birth, the zona glomerulosa (aldosterone) and fasciculata (cortisol) are present; however, the zona reticularis (sex hormones) is not established until 3 years of age.
- Medulla = ***neural crest cells (sympathetic ganglion)***
- Relatively larger in children than adults; due to large cortex at birth
- Located ***within Gerota's fascia***
- The adrenal gland is from a totally different embryologic origin than the kidney; therefore, neither renal agenesis nor renal malposition affects adrenal development and location.

| RENAL |

PRONEPHROS (WEEK 4)

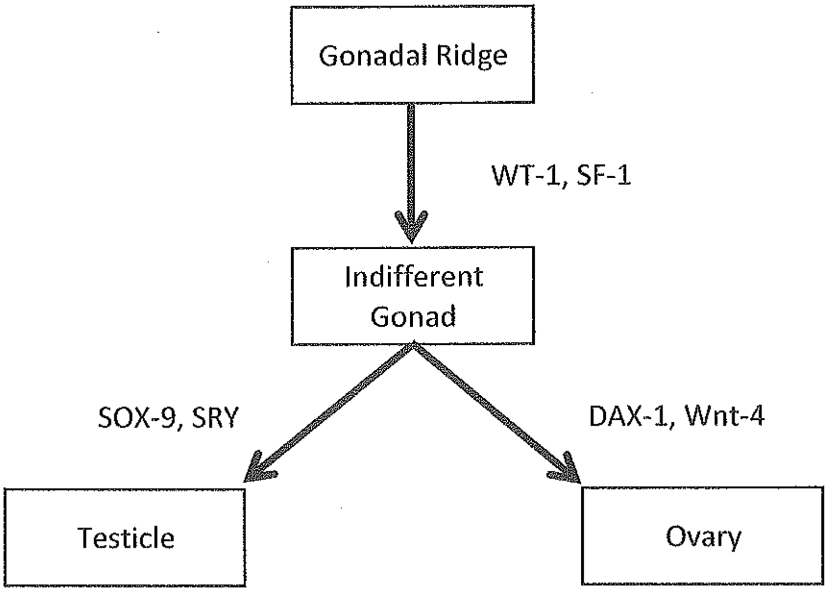
- Transient and nonfunctional
- Develops caudally toward the cloaca
- Disappears leaving behind the pronephric duct

MESONEPHROS (WEEK 4-8)

- Interim function
- Joins the pronephric duct to yield the ***mesonephric duct (Wolffian duct)***, which opens into the cloaca
- The ureteric bud (aka ***metanephric diverticulum***) forms during week 5 via a diverticulum off the mesonephric duct
    - ***There is an association between the clinical findings of an absent vas deferens and ipsilateral renal agenesis. The mesonephric (Wolffian) duct is the common problem.***
- ***Paramesonephric ducts*** develop lateral to the mesonephric duct and gonads
    - These ducts are critical for female reproductive organs

METANEPHROS (FUNCTIONAL AROUND WEEK 9)

- Ureteric bud moves cranially and penetrates the metanephrogenic blastema



-
    - ***Ureteric bud = ureter, renal pelvis, calices, collecting tubules***

  - ***Metanephrogenic blastema = nephron*** (glomerulus, proximal tubule, loop of Henle and distal tubule)
- As the ureteric bud is branching near the cloaca, caudally it is absorbed into the genitourinary sinus (i.e. bladder)
- The pelvic forming kidney ascends to the L1/T12 position and rotates in an orientation similar to that of the psoas muscle.
- The kidney is undergoing revascularization throughout its ascent

| BLADDER / URETHRA |

CLOACA

- A common cavity with merging of genitourinary and intestinal systems.
- The cloaca is distal ***hind gut*** (endoderm)
- By the 7th week, the cloaca is divided by the urorectum septum creating an anterior ***urogenital sinus*** and posterior ***rectum***

UROGENITAL SINUS (STARTS 8TH WEEK)

- "Anterior cloaca" composed of endoderm
- Divided into upper (bladder), pelvic (prostatic urethra and entire female urethra) and phallic (genital tubercle, distal male urethra)
- NOTE: the verumontanum is the location where the Wolffian ducts fuse to the urogenital sinus

BLADDER (WEEKS 9-12)

- "Upper anterior cloaca" mostly composed of endoderm
- Trigone, ureteric orifice and ejaculatory ducts are derived from ***mesoderm (via mesonephros)***, while the rest of bladder is ***endoderm (via urogenital sinus)***
  - In females the entire floor of urethra is also mesoderm
- Allantois becomes urachus around week 12, which becomes the ***median umbilical ligament*** in the adult
  - ***Adenocarcinoma*** of the urachus is seen at the dome of the bladder and is one of the few indications for partial cystectomy

| GONADS |

- In females, the mesonephric (Wolffian) duct regresses in response to a lack of testosterone, and the ***paramesonephric (Mullerian) duct*** persists to form the ***uterus, fallopian tubes,*** and ***superior 1/3 of the vagina***

INDIFFERENT GONAD

- During week 5, medial to the bilateral mesonephros, a ***gonadal ridge*** is formed from germinal epithelial cells and mesenchyme under genetic influence of ***Wilms Tumor (WT1)*** and ***Steroidogenic factor-1 (SF-1)***
- The following week, primordial germ cells migrate into the mesenchyme forming ***primary sex cords***, thus the indifferent gonad is developed
- The indifferent gonad has a ***cortex*** (forms the ***ovary***; regresses in males) and ***medulla*** (forms the ***testicle***; regresses in females)

Gender specific origin from the Indifferent gonad

Medulla in Men;

The 'O' in cOrtex is for Ovary

- The indifferent gonad is influenced to become a **testicle** by the genes: ***SOX-9*** (SRY-related HMG box) and ***SRY*** (Sex-determining region Y), while the ***ovary*** is genetically influenced by ***Wnt-4*** (wingless-related MMTV integration site 4) and ***DAX-1*** (Dosage-sensitive sex-reversal adrenal hypoplasia congenital-critical region of the X chromosome, gene 1)

TESTES (STARTS WEEK 7)

- The ***SRY gene*** is located on ***Yp11.3*** (short arm of the Y chromosome); required for testosterone production and ultimately, testicular development

- Primary sex cords of the indifferent gonad condense into the gonadal medulla to form the rete testis and seminiferous cords
- The tunica albuginea development encases the seminiferous cords to form the testicle
- Seminiferous cords become seminiferous tubules, tubular recti, rete testes
    - Seminiferous tubules lack a lumen until puberty
- ***Interstitial cells of Leydig*** develop between seminiferous tubules
    - Secretes testosterone and androstenedione by the 8th week.

Testicular Cells

Leydig cells secrete testosterone,

Sertoli cells do everything else

- **Sertoli cells** line the seminiferous tubules and secrete ***Mullerian Inhibiting Substance (MIS)*** causing the paramesonephric (Mullerian) ducts to regress
- Then the mesonephric (Wolffian) ducts migrate caudally to form the ***Seminal vesicles, Ejaculatory ducts, Epididymis, Efferent ductules, Ductus deferens*** under the influence of ***testosterone***
    - Local testosterone is necessary for Wolffian duct development!!! Many sex hormones have a ***paracrine function***, which results in contralateral structures differing, particularly with intersex disorders.

Acronym for Wolffian Structures

"Wolffian structures require testosterone for males to plant their SEEED"

- During the 9th week, ***efferent ductules*** appear as outpouchings from the epididymis (i.e. mesonephric / Wolffian duct) ***connect to the rete testis*** (i.e. gonads) to establish the first genitourinary connection

- The testicular attachment to the mesonephros becomes mesorchium, and then by the 8 month, the testicle descends into the scrotum with guidance from the ***gubernaculum***
- While passing through the inguinal canal, the testicle takes a piece of peritoneum (***processus vaginalis***) into the scrotum which forms the ***tunica vaginalis***
    - If the processus vaginalis is patent, peritoneal fluid may flow into the area surrounding the testicle and cause a ***communicating hydrocele,*** which may also contain visceral organ(s) (i.e. ***congenital inguinal hernia***)
- Majority of hydroceles in infancy will resolve spontaneously

OVARY (STARTS WEEK 8-9)

- If testicles do not developed, a definitive ovary with begin to develop (i.e. default development)
- Primitive sex cords join the indifferent gonadal medulla, which ultimately regresses
- The female **gonadal surface epithelium *(cortex)*** proliferates and then generates cortical cords, which extend into the underlying mesenchyme
- At 4 months, the cortical cords divide into isolated cell clusters known as ***primordial follicles*** (oogonia and follicular cells)
- The ***oogonia*** then undergo ***mitosis*** to produce more primordial follicles and ultimately primary oocytes
    - All oogonia are formed while a fetus - the surface epithelium deteriorates at birth
- Females are born with approximately two million ***primary oocytes*** arrested in ***Prophase I of meiosis I*** until menarche
    - At puberty FSH stimulates a few primary oocytes to re-enter meiosis until one dominate follicle enters ovulation, normally on a monthly basis

| GENITALS |

INDIFFERENT GENITALIA (WEEKS 4-7)

- At the 4th week, a ***genital tubercle*** is formed on the cloacal membrane with ***labioscrotal swellings*** and ***urogenital folds*** developing bilaterally to the tubercle
- The genital tubercle elongates to form the ***primordial phallus***
- Genital tubercle → primordial phallus → ***glans penis*** or ***clitoris*** (under hormonal stimulation during weeks 9-12)

PENIS (WEEKS 9-12)

- Masculinization of the primordial phallus via ***DHT*** (dihydrotestosterone)
- The ***urogenital folds*** nearly surround the ***urethral plate*** (endoderm), except at the future site of the penile raphe, which creates a ***urethral groove***
- Then the urogenital folds completely fuse resulting in invagination and tubularization of the urethral plate / groove to form the ***spongy urethra***
    - NOTE: The urogenital fold is covered by ectoderm (penile skin) and fuses to form the ***penile raphe*** as the urogenital folds fuse
    - Penile mesenchyme forms the corpus cavernosum / spongiosum
- During the 11th week at the glans penis, an ***ectodermal cord*** (essentially invagination of ectoderm / penile skin) forms to travel proximally and join the spongy urethra; this forms the ***fossa navicularis / urethral meatus***
    - If the spongy urethra does not meet with the ectodermal cord, a ***hypospadias*** will develop
- During the 12th week, the ectoderm also has a circular ingrowth around the glans to form the ***prepuce***
- The ***labioscrotal swellings*** fuse in the midline to from the ***scrotum***
    - If a hemiscrotum is hypoplastic, an ***undescended testicle*** is likely present

FEMALE

- Feminization of the primordial phallus via ***estrogens*** form the ***clitoris***
- ***Urogenital folds*** only fold posteriorly (labia minora frenulum) resulting in the unfused portions becoming the ***labia minora***
- ***Labioscrotal folds*** fuse posteriorly and anteriorly (labial commissures and mons pubis) resulting in the unfused portions becoming the ***labia majora***

| ACCESSORY GENITAL STRUCTURES |

BULBOURETHRAL (COWPER OR BARTHOLIN) GLANDS

- Forms as buds from the urethra (urogenital sinus)
- Males: ***Cowper's glands*** produces the pre-ejaculate that neutralizes the pH of the urethra and lubricates it for seminal ejaculation
    - Located at the membranous urethra with ducts entering the urethral bulb
- Females: ***Bartholin's glands*** produce vaginal lubrication
    - Located at 5 and 7 o'clock position relative to the vaginal introitus

PROSTATE (12TH WEEK)

- Formed from the pelvic portion of the ***urogenital sinus*** under stimulation of ***DHT***
- Paired epithelial buds (glands) arise from the urethra (urogenital sinus) and enter the surrounding mesenchyme (stroma)
- NOTE: the female analogous structures are the ***Skene's glands***, located within the vulva at 4 and 8 o'clock relative to the urethra

MALE HORMONAL DEVELOPMENT

Testosterone	Dihydrotestosterone
Mesonephric (Wolffian) Duct seminal vesicles ejaculatory ducts epididymis efferent ductules ductus deferens	***Urogenital Sinus*** prostate penis scrotum

UTERUS / FALLOPIAN TUBES / VAGINA

- In the absence of MIS, the ***paramesonephric ducts*** will further develop
- The paramesonephric ducts fuse caudally to form the ***uterovaginal primordium*** (uterus and upper vagina), while the cranial unfused portions become the ***uterine tubes*** (fallopian tubes)
    - o This fusion also creates the ***broad ligament***
- The lower vagina is formed from the ***urogenital sinus***, which joins with the ***uterovaginal primordium*** to form the ***sinus tubercle*** and then a pair of ***sinovaginal bulbs***
- Fusion of the sinovaginal bulbs forms the ***vaginal plate***
    - o The center cells degrade creating a vaginal lumen, while the peripheral cells form the vaginal mucosa
- The ***hymen*** is an invagination of the urogenital sinus posterior wall
- The ***round ligament*** passes through the inguinal canal to join the labia majora (just as the testicles/gubernaculum descend into the scrotum) during ovarian descent into the pelvis. If the female has a persistent processus vaginalis, it is called the ***canal of Nuck***

SUMMARY OF EMBRYOLOGIC STRUCTURES AND VESTIGIAL REMNANTS

Embryologic Structure	**Male**	**Female**
Mesonephric Tubules	Testicular efferent ductules	*Epoophoron*
	Paradidymis	*Paroophoron*
Mesonephric Duct	*Appendix epididymis*	Appendix vesiculosa
	Epididymis Vas deferens	*Gartner's Duct*
	Ureter, renal pelvic, calices, collecting tubes	Ureter, renal pelvic, calices, collecting tubes
Paramesonephric Duct	*Appendix testis (Hydatid of Morgagni)*	Fallopian tubes
	Prostatic utricle (lined by urogenital sinus)	Uterus and upper vagina
Urogenital Sinus	Bladder, urethra	Bladder, urethra
	Prostate	Skene's (paraurethral) glands
	Cowper's gland	Bartholin's glands

Embryologic Structure	Male	Female
Sinus Tubercle	Verumontanum (seminal colliculus)	Hymen
Gubernaculum	Gubernaculum	Round ligament
Phallus	Glans penis	Clitoris
Urogenital folds	Ventral penis	Labia minora
Labioscrotal swellings	Scrotum	Labia majora

* *Vestigial remnants are italicized.*

CHAPTER 2: ANATOMY

| SKELETAL SYSTEM |

SPINAL COLUMN

- Thoracolumbar spinal nerves are named for the vertebral body above the exiting foramen
- **Spinal cord**: in adults = terminates at L1-L2 vertebrae; in newborns = terminates at L3 vertebrae (ascends with age)

RIBS

- Left kidney: protected by ribs 11 & 12
- Right kidney: protected by rib 12 (sits lower due to liver)
- Flank nephrectomies may require 11th or 12th rib resection, which may result in a high risk for flank incision hernias
    - Flank incision hernia is secondary to a costal neurovascular bundle injury

Costal Neurovascular Bundle

Runs along the inferior rib border between the ***internal oblique muscle*** and ***transversus abdominis***

PELVIS

- **True pelvis (Lesser pelvis)**: circumferentially around the pelvic brim and pubic symphysis extending inferior to the pelvic floor (i.e. levator ani)
    - Contains bladder, rectum, uterus, vagina, prostate, seminal vesicles
- **False pelvis (Greater pelvis)**: area superior to the true pelvis between iliac wings
    - Contains small bowel and sigmoid colon
- **Obturator foramen**: the bilateral "holes" formed by the ischium and pubic bones; majority of the foramen is occluded by the obturator membrane
- **Obturator canal**: superolateral region of the obturator foramen; the obturator artery, vein, and nerve travel through this canal
    - Avoid this area during a transobturator sling as it may result in a neurovascular injury to the adductor muscle group
- **Ischial spine**: palpate during a vaginal cystocele repair, and then the suture is passed through the sacrospinous ligament (ligament between sacrum and ischial spine)
- **Urogenital Triangle**: anterior perineum; pubic symphysis (vertex) down to bilateral ischial tuberosities
- **Anal triangle**: posterior perineum; coccyx bone (vertex) up to bilateral ischial tuberosities
- Sacrum ***S3 foramen***: location for neuromodulation stimulation
- ***Scimitar sacrum***: highly suggestive of ***anterior sacral meningocele***
- ***Sacral agenesis***: associated with ***maternal diabetes***

| MUSCLES |

ABDOMINAL WALL LAYERS

- ***Arcuate line***: runs transversely, and located slightly caudal to the umbilicus
    - Inferior / Superior epigastric vessels change name at this point

RECTUS SHEATH (ANTERIOR ABDOMINAL WALL)

ABOVE the Arcuate Line	BELOW the Arcuate Line
External oblique fascia Internal oblique fascia (1/2)	External oblique fascia Internal oblique fascia Transversus abdominis fascia
Rectus muscle	Rectus muscle
Internal oblique fascia (1/2) Transversus abdominis fascia Transversalis fascia Preperitoneal fat Peritoneum	Transversalis fascia Preperitoneal fat Peritoneum

- **Posterior abdominal wall**
  - Outer posterior layer: Latissimus dorsi - external oblique
    - ***Latissimus dorsi is the first muscle incised during flank incisions***
  - Middle posterior layer: internal oblique, serratus (posterior and inferior), sacrospinalis
  - Inner posterior layer: quadratus lumborum, iliacus
  - Innermost posterior layer: psoas, diaphragm
- **Flank incision layers**: external oblique - internal oblique - NVB - transversus abdominis - transversalis fascia - thoracolumbar fascia - pararenal tissue / fat - Gerota's fascia - perirenal fat – kidney
- **Levator ani**: puborectalis, pubococcygeus, iliococcygeus
- **Inguinal canal**: external oblique (anterior), transversus abdominis (floor), inguinal ligament (inferior)
- **Femoral triangle**: inguinal ligament (superior), sartorius (lateral), adductor longus (medial)

Femoral Triangle Contents Acronym

NAVEL Ship (lateral to medial):

Nerve / Artery / Vein / hErnia / Lymphatic / Scrotum

ABDOMINAL WALL LIGAMENTS

- **Medial umbilical ligaments** = fetal umbilical artery remnants
    - Origin: ***hypogastric artery***
    - Important laparoscopic surgical landmark as the ureters run medial to the medial umbilical ligaments
- **Median umbilical ligament** = urachus remnant
- **Falciform ligament** = fetal umbilical vein remnant

| VESSELS |

ABDOMINAL AORTIC BRANCHES (TOP TO BOTTOM)

- Inferior phrenic, celiac, SMA, middle adrenal, renal, gonadal, lumbar (L1-L4), IMA, common iliacs (L4), medial sacral
    - Lumbar branch can be a source of serious bleeding during an RPLND

GASTROINTESTINAL BLOOD SUPPLY

- Celiac (foregut): liver, spleen, stomach, proximal duodenum, pancreas
- SMA (midgut): distal duodenum, jejunum, appendix (ileocecal), right colon, 2/3 of transverse colon (middle colic)
- IMA (hindgut): 1/3 transverse colon, descending colon (left colic), sigmoid (sigmoid), superior rectum (***superior hemorrhoidal***)
    - Artery that inhibits horseshoe kidney ascension
    - Marginal artery of Drummond: anastomotic arc between SMA and IMA

- Middle hemorrhoidal: middle rectum (***inferior vesical*** from internal iliac)
- Inferior hemorrhoidal: inferior rectum (***internal pudendal*** from internal iliac)

ILIAC (HYPOGASTRIC) BRANCHES

- External iliac: inferior epigastric (medial), deep circumflex (lateral), femoral (terminal)
  - Deep circumflex vein is distal extent of a classic pelvic lymph node dissection
- Internal iliac
  - Posterior: iliolumbar, lateral sacral, superior gluteal

> If you need ligate the hypogastric for uncontrolled pelvic bleeding, do it ***distal to the posterior internal iliac branch***

  - Anterior: obturator, obliterated umbilical artery (medial umbilical ligament), umbilical artery usually branches to superior vesical, sometimes direct from iliac, [women - uterine, vaginal], inferior vesical, middle rectal, internal pudendal
    - **Alcock's canal**: internal pudendal artery, nerve and vein leave the pelvis
    - Protects neurovascular bundle that is responsible for penile sensation during a radical prostatectomy
- Vessel at greatest risk for umbilical laparoscopic port placement: ***right common iliac artery*** followed by the aorta (iliac veins are posterior to arteries)

| NEUROLOGY |

PITUITARY GLAND

Anterior pituitary (Adenohypophysis)		
Abbreviation	**Hormone**	**Activity**
ACTH	Adrenocorticotropic hormone (corticotropin)	Cortisol release (adrenal cortex)
FSH	Follicle-stimulating hormone	Spermatogenesis (Sertoli cell)
LH	Luteinizing hormone	Testosterone release (Leydig cell)
TSH	Thyroid-stimulating hormone	Thyroxine (T4) and Triiodothyronine (T3) release (thyroid)
GH	Growth hormone	Stimulates cell growth / regeneration
PRL	Prolactin	Lactation (breasts), inhibits dopamine and GnRH
MSH	Melanocyte-stimulating hormones	Skin darkening by melanin release (melanocytes)
Posterior pituitary (Neurohypophysis)		
Abbreviation	**Hormone**	**Activity**
ADH	Anti-diuretic hormone (Vasopressin)	Increase renal water reabsorption (collecting duct); vessel constriction
OXT	Oxytocin	Uterine contraction

NOTE: *the hypothalamus communicates with the anterior and posterior pituitary via vascular and neuronal pathways, respectively. Mnemonic: the heart (vascular) in anterior and the spinal cord (neuronal) is posterior.*

NERVE ORIGIN AND FUNCTION

Nerve	Root	Function *	Notes
Iliohypogastric	L1	S: lower abdominal wall, pubic area M: lower abdominal wall	
Ilioinguinal	L1	S: anterior scrotum / labia, base of penis, upper thigh	enters transversalis fascia just prior internal inguinal ring then joins cord structures
Genitofemoral	L1-2	S: cord, scrotum / labia, anterior thigh M: cremaster	travels anterior to psoas muscle, may injury with psoas hitch; runs posterior to spermatic cord; MC injury during laparoscopic varicocelectomy (~ 5%)
Lateral femoral cutaneous	L2-3	S: anterior / lateral portion of thigh	runs at least 3cm lateral to internal inguinal ring
Obturator	L 2-4	S: posterior thigh M: leg adduction	may be stimulated with lateral TURBT; injured during PLND or TOT
Femoral	L2-4	S: anterior / medial thigh M: psoas, hamstrings	runs posterior to psoas
Common Peroneal	L4 - S2	S: lower leg / foot M: dorsiflexion of foot	most likely injured nerve during lithotomy position, results in foot drop

Nerve	Root	Function *	Notes
Pudendal	S2-4 (Onuf's nucleus)	S: penis / clitoris, posterior scrotum M: external urinary sphincter, ejaculation	bulbocavernosus reflex utilizes this nerve

** Function: S = sensation, M = motor*

| ADRENAL GLANDS |

STRUCTURE

- **Cortex** ("GFR - salt, sugar, sex") - mesoderm
    - Zona Glomerulosa: Aldosterone (stimulated by RAAS)
        - * Renin → Angiotensinogen → Angiotensin I → Angiotensin II → Aldosterone + ADH
    - Zona Fasciculata: Glucocorticoids (cortisol, stimulated by ACTH)
        - * CRH → POMC → ACTH → Cortisol
    - Zona Reticularis: DHEA, androstenedione (stimulated by LH)
- **Medulla** = neural crest cells
    - Epinephrine and norepinephrine (stimulated by sympathetic nervous system)
    - Tyrosine → L-DOPA → Dopamine → Norepinephrine → Epinephrine
        - * Phenylethanolamine-N-methyltransferase (PNMT) converts norepinephrine to epinephrine; found only in adrenal medulla

Neuroblastoma only has norepinephrine;

Pheochromocytoma has both norepinephrine and epinephrine

    - * Catecholamine degradation via catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO)
- ***Adrenal glands are located within Gerota's fascia***

VASCULATURE / LYMPHATICS

- **Artery**: inferior phrenic (superior), aorta (middle), renal artery (inferior)
    - * ***Vein***: right - empties into IVC posteriorly (***short; common source of bleeding during adrenalectomy and nephrectomy***), left - empties into left renal vein opposite of left gonadal vein
- **Lymphatics**: follows arterial / venous supply

| KIDNEY |

STRUCTURE

- **Cortex** = glomerulus, proximal tubule, distal tubule
    - o ***Macula densa*** located in the wall of the ***distal tubule*** to sense changes in sodium and chloride
    - o **Column of Bertin**: cortex that extends between the renal pyramids
- **Medulla** (renal pyramids) = loop of Henle, collecting duct
    - o Renal papillae are vertex of the medullary renal pyramids
        - * Renal papillary necrosis: usually from ischemic conditions (medulla is the last area of the kidney to receive blood from

the renal artery)

- **Gerota's Fascia** - surrounds kidney and adrenal; open inferiorly to retroperitoneum
    - Anterior leaf = Toldt's fascia
    - Posterior leaf = Zuckerkandl's fascia
    - ***Pararenal*** fat = fat ***outside Gerota's fascia***
    - ***Perirenal*** fat = fat ***inside Gerota's fascia*** (applies to hematomas as well)
    - Renal capsule = direct attachment to renal parenchyma
- ***Pacemaker cells in calyces create peristalsis of the ureter, not neuronal innervation.*** This is why transplant kidneys have ureteral peristalsis.
- Posteriorly the kidneys rest against the diaphragm and quadratus lumborum.

VASCULATURE / LYMPHATICS

- **Artery**: renal artery - segmental - interlobar - arcuate - interlobular - afferent arterioles - glomerulus - efferent arterioles
    - ***1st renal artery branch: posterior segmental*** (other segments include apical, upper, middle, inferior)
    - ***Juxtaglomerular cells:*** located within the wall of the ***afferent arteriole*** and produce / secrete renin.
- **Vein**: short right renal vein to IVC; long left renal vein that normally crosses anterior to the aorta

> Prefer left kidney for renal transplant because of longer renal vein

-
    - ***Lumbar veins*** are encounter more often on the ***left*** and posterior to the kidney. May be source of serious bleeding during nephrectomy.
- **Lymphatics**: kidney and testicle have identical drainage zones

| URETER |

STRUCTURE

- **Ureteral bud** forms: collecting duct - fornix (renal pyramid's papilla connection) - minor calyx - major calyx - infundibulum - renal pelvis - ureter - ureteral orifice
    - See embryology for further details
- May routinely be located anterior to the bifurcation of the common iliac.
- The ureter runs along the psoas muscle majority of the way into the pelvis.

"Water under the bridge"

The ureters pass posterior to the vas deferens / uterine arteries

- Superiorly: the ureter is lateral to the gonadal vessels
- Distally: the ureter crosses over, and lies medial the gonadal vessels
    - NOTE: the kidney is lateral so the ureter must move medial to join with the bladder
- The renal pelvis and proximal ureter has 2 layers: longitudinal and circular, which increases to 3 layers in the distal ureter: external longitudinal, a middle circular, and an internal longitudinal
    - The proximal, thinner ureter is more prone to endoscopic perforation
- **Waldeyer's sheath**: smooth muscle layer of the ureter that joins it to the trigone
- **Chwalla's Membrane**: location where the ureter must perforate the trigone, if not then a ureterocele occurs
- **Retrocaval ureter**
    - Secondary to persistent ***right subcardinal vein*** during development

  - Right ureter courses behind and medial to the IVC
- **Weigert-Meyer Rule:** valid in duplex / duplicated ureteral systems
  - Upper pole = ureteral orifice inferior and medial; ***ureterocele, hydronephrosis***; may be ectopic
  - Lower pole = ureteral orifice superior and lateral; ***VUR***
  - **Drooping lily sign** = hydronephrotic/obstructed nonfunctioning upper pole shifts the lower opacified pole to appear as a drooping lily
  - Most common renal abnormality = ureteral duplication

VASCULATURE

- Proximally = medial vasculature from aorta / IVC
- Distally = lateral vasculature from iliac vessels

| BLADDER |

STRUCTURE

- Trigone = mesoderm (origin: ureteric buds)
- Bladder = endoderm (origin: urogenital sinus / hindgut)
- Urachus located at the dome of the bladder
  - **Patent urachus**: drainage into umbilicus
  - **Urachal sinus**: tracts from umbilicus but stops prior to the bladder
  - **Urachal cyst**: no connection to umbilicus or bladder
- **Urothelium layers**: GAG - Uroplakins (apical membrane) - umbrella cell - intermediate cell - basal cell
  - 5-7 cell layers thick in contracted bladder, 2-3 cells thick in distended bladder
  - ***Potassium sensitivity test***: 400mM potassium chloride solution infused in the bladder. If the urothelium is inflamed, pathologic permeability results in bladder irritation and pain from the potassium.

- **Urothelium and Uroplakins (UP)**
  - UPIa associates with UPIII and UPIb associates with UPII.
  - Each subunit is then composed of an inner ring of six proteins (UPIa or UPIb) and an outer ring of six proteins (UPII or UPIII).
  - 1000 uroplakin-rings make up a single "plaque" with "hinges" separating it from adjacent plaques. All the plaques together form the scallop-shaped apical membrane of the umbrella cells of the urothelium.
    - Umbrella cells are joined together by tight junctions.
  - Cell replacement is by fusion of the basal cell layer to form intermediate cells and fusion of intermediate cells to form umbrella cells

Uropathogenic E. coli (UPEC) – Type 1 Pileated

Attach to the uroplakins and leads to umbrella cell apoptosis

- **Umbrella cell**
  - Radiation / infectious cystitis disrupts umbrella cells
- **von Brunn's Nests**
  - Reactive proliferative change in majority of benign bladders within the lamina propria

VASCULATURE / INNERVATION

- **Artery**
  - Superior vesical - anterior branch of the internal iliac at bifurcation of obliterated umbilical artery; occasionally directly from the internal iliac
    - During psoas hitch, may sacrifice contralateral pedicle to allow for less bladder tension
  - Inferior vesical - anterior branch of the internal iliac

- **Innervation**
    - **Sympathetic**: T11-L2, hypogastric nerve, (alpha receptors: trigone, bladder neck; beta 3 receptors: bladder body)
    - **Parasympathetic**: S2-S4, pelvic nerve (muscarinic receptors: bladder body)

Parasympathetic Receptors

M2 receptors are more prevalent; however, ***M3 receptors*** are more important for ***bladder contraction***.

-
    - **Somatic**: S2-4, pudendal nerve (external sphincter)
- Detrusor nerve fibers
    - **Alpha-delta fiber**: sensation of stretch; ***myelinated***
    - **C-fiber**: sensation of pain; ***unmyelinated*** (pathologic)

Acronym for C-fibers

CUP biopsies may hurt

C = c fiber, ***U*** = unmyelinated, ***P*** = pain

| PROSTATE |

STRUCTURE

- **Central Zone**
    - Cone shaped, surrounds ejaculatory ducts
    - 25% of glandular tissue
    - 1-5% of prostatic cancer

- **Peripheral**
  - Posterior / lateral prostate
  - 70% of glandular tissue
  - 70-80% of ***prostatic adenocarcinoma***
- **Transitional**
  - 5% of glandular tissue
  - 10-20% of prostatic adenocarcinoma
  - Main site of ***BPH and median lobe***
- **Anterior fibromuscular stroma**
  - 5% of glandular tissue

VASCULATURE / INNERVATION

- Neurovascular bundles run posterior / lateral to the prostate from the base to the apex
  - Lies between ***levator*** and ***prostatic fascia***; ***Denonvilliers' fascia*** is inferior to the bundles
- **Artery**: prostatic branch of inferior vesical artery
  - Seen on cystourethroscopy at 5 and 7 o'clock positions
- ***Batson's plexus***: vertebral veins that communicate with pelvic veins and DVC
  - Etiology of ***spinal metastasis***
- **Nerves**:
  - Sympathetic: ***hypogastric nerve (T10-L2)***
  - Parasympathetic: ***pelvic nerve (S2-S4)***

| URETHRA |

STRUCTURE

- **Posterior**: prostatic and membranous
- **Anterior**: bulbar, penile, glanular (fossa navicularis)
  - Completely encircled by the corpus spongiosum

- In females, distal 1/3 may be excised without affecting continence
- Inner longitudinal and outer circular muscle fibers
- **Urethral epithelium**
    - Prostatic and membranous = ***transitional***
    - Bulb and pendulous = ***pseudostratified columnar***
    - Fossa navicularis = ***stratified squamous***
- **Glands of Littre**
    - Tubuloacinar, mucinous glands within the urethra
- **Lacunae of Morgagni**
    - Intraepithelial glands; urethral mucosa depressions
        - Largest in fossa navicularis called Lacuna Magna
- See penis anatomy section for surrounding fascial layers
- **Cowper's glands**
    - Cowper's gland: located in the urogenital membrane adjacent to the membranous urethra
    - Cowper's ducts: extend from the gland to urethral bulb
    - ***Urethral diverticulum***: in a young male, MC etiology is dilation of a Cowper's gland duct

VASCULATURE / LYMPHATICS

- **Corpus spongiosum arterial supply**
    - Internal pudendal artery → ***common penile artery*** → bulbourethral artery
- **Lymphatics**
    - ***Distal urethra***: superficial then deep inguinal lymph nodes (separated by fascia lata)
    - ***Proximal urethra***: external iliac then hypogastric/obturator nodes

| PENIS |

STRUCTURE

- Layers: skin - Dartos fascia - superficial dorsal vein - Buck's fascia - Dorsal neurovascular bundle - tunica albuginea - corpus cavernosa - cavernosal artery
  - o **Dartos** and **Bucks' fascia** surround the entire penis including the urethra
    - * During circumcision, the prepuce and underlying Dartos are removed; do not violate Buck's fascia.
    - * ***Penile fracture***: if Buck's fascia is intact (i.e. only rupture of the tunica albuginea) then only the patient's penis is ecchymotic (***eggplant deformity***). If Buck's fascia is violated then the scrotum, penis, and perineum may have ecchymosis because it is contained by Dartos / Colles' fascia.
  - o ***Tunica albuginea*** only surrounds the corpus cavernosa with a midline septa.
  - o The urethra is surrounded by the ***corpus spongiosum***, which forms the penile glans.
    - * A straddle injury to the anterior urethra that violates Buck's fascia will cause a ***butterfly hematoma*** to the perineum because the hematoma is contained in Colles fascia in the superficial perineum.
    - * Posterior urethral injuries are usually associated with pelvic fracture, especially inferior rami fractures and pubic symphysis diastasis

VASCULATURE / INNERVATION

- ***Internal pudendal artery*** penile branches include:
  - o **Bulbar artery** - bulb / glans
  - o **Urethral artery** - corpus spongiosum, urethra, glans penis
  - o ***Common penile artery*** - corpus cavernosum: important for erections
    - * ***Dorsal penile artery***: on penile shaft beneath Buck's

fascia near the 12 o'clock position

        - ***Cavernosal artery*** (aka deep penile artery): within the middle of both corpus cavernosum

- ***External pudendal artery***: supplies the penile skin and prepuce
- ***Accessory pudendal artery***: found in ~ 25% of people; courses lateral to prostate
    - Unilateral or bilateral
    - Critical to spare during prostatectomy as it provides up to ~ 25% of penile blood flow
- **Dorsal NVB** (deep dorsal vein / dorsal penile artery / dorsal nerve of the penis)
    - Lies between Buck's and tunica albuginea
    - ***Dorsal nerve of the penis: pudendal*** (S2-S4); penile somatic sensation
- **Cavernous nerves**
    - ***Parasympathetic*** fibers via ***pelvic nerve (S2-S4)*** for tumescence
        - Injured during abdominal perineal resection (APR)
- **Hypogastric nerves**
    - ***Sympathetic*** fibers via T10-L2 for detumescence
        - Injured during an RPLND

Penile Tumescence

Dorsal penile artery

Deep penile artery (aka Cavernosal artery)

| TESTICLE |

STRUCTURE

- Sperm Pathway: seminiferous tubules - rete testes - efferent ductules - epididymal head then tail - vas deferens
- **Sertoli cells**: epithelium of the seminiferous tubules acting as a "nurse cell"
    - o Secrete ***Mullerian Inhibiting Substance*** as a fetus to regress paramesonephric ducts
    - o Support ***spermatogenesis*** in response to ***FSH***
    - o Secrete ***inhibin*** to down-regulate ***FSH*** production from the anterior pituitary
    - o Maintain ***blood-testis barrier***
    - o Secrete ***androgen binding protein*** to increase testosterone concentrations in seminiferous tubules to allow spermatogenesis
- **Leydig cells**: adjacent to seminiferous tubules (i.e. interstitial cells of Leydig)
    - o Secrete ***testosterone*** in response to ***LH*** from the anterior pituitary
    - o "Leydig cells secrete testosterone, and Sertoli cells do everything else."
    - o Histology: ***Reinke crystals*** (rod shaped crystals) are seen in Leydig cells
- ***Hydatid of Morgagni*** = appendix testes = mullerian duct remnant (upper pole of testes)

TESTICULAR VASCULATURE / INNERVATION

Testicular Arterial Supply	Alternative Name	Origin
Testicular	Internal Spermatic	Aorta
Vasal	Differential	Superior vesical (occasionally anterior internal iliac)
Cremasteric	External Spermatic	Inferior epigastric

NOTE:

- **Epididymis**
  - Superior epididymal (origin = testicular artery)
  - Inferior epididymal (origin = deferential artery)
- **Seminal Vesicles**
  - Vesicodeferential (origin = internal iliac)

| SCROTUM |

SCROTAL LAYERS AND ASSOCIATED CONTRIBUTIONS

Scrotum	Abdominal Wall Contributions	Penis
Skin	Skin	Skin
Dartos fascia (Colles' fascia = perineum)	Scarpa's fascia	Dartos fascia
External spermatic fascia	External abdominal oblique	Buck's fascia Not contiguous
Cremaster muscles (supplied by genitofemoral nerve)	Internal abdominal oblique, and sometimes transversus abdominis	
Internal spermatic fascia	Transversalis fascia	
Visceral tunica vaginalis	Peritoneum	
Parietal tunica vaginalis	Peritoneum	

| PREGNANCY-RELATED CHANGES |

- ***Hydronephrosis***: (1) mechanical compression of the ureteral by the enlarging uterus (2) increased progesterone leads to decreased smooth muscle contract (i.e. decreased peristalsis)
    - *o* Most commonly seen in the right ureter
- ***Increased GFR / plasma renal flow***: normal pregnancy values:
    - *o* Creatinine ≤ 0.8
    - *o* BUN ≤ 13
    - *o* Proteinuria ≤ 300mg / day
- ***Overactive bladder***: bladder displacement and irritation by the enlarging uterus
- ***Bacteriuria*** (usually asymptomatic): much higher incidence of pyelonephritis than non-pregnant women with asymptomatic bacteria
    - *o* Screen all women in the 1st trimester with urine culture
    - *o* All bacteriuria, asymptomatic or symptomatic, should be treated in pregnant women
    - *o* If the female develops pyelonephritis, IV antibiotics, hydration, and hospitalization are initially required

QUICK REFERENCE TABLE FOR ARTERIAL SUPPLY

Organ	Artery	Origin Artery
Adrenal	Superior adrenal	Inferior epigastric
	Middle adrenal	Aorta
	Inferior adrenal	Renal
Renal	Renal	Aorta
Ureter	Superiorly	Renal / Aorta
	Inferiorly	Iliac

Organ	Artery	Origin Artery
Bladder	Superior vesical	Anterior branch of the internal iliac
	Inferior vesical	Anterior branch of the internal iliac
Prostate	Prostatic branch	Inferior vesical
Urethra	Bulbourethral	Common penile
	Urethral	Internal pudendal
Penis	Bulbar	Internal pudendal
	Urethral	Internal pudendal
	Common penile	Internal pudendal
Clitoris	Dorsal artery of the clitoris	Internal pudendal
Testicle	Testicular (Internal spermatic)	Aorta
	Vasal (Deferential)	Superior vesical
	Cremasteric (External spermatic)	Inferior epigastric
Epididymis	Superior epididymal	Testicular
	Inferior epididymal	Vasal
Seminal Vesical	Vesicodeferential	Internal iliac
Labia / Vulva	External pudendal	Femoral
	Labial	Internal pudendal

CHAPTER 3: UROGENITAL ANOMALIES

| RENAL |

RENAL AGENESIS

- Lack of ureteric bud or failure to interact with metanephric blastema
- **Bilateral renal agenesis**
    - Majority of infants are stillborn or die within 48 hours (respiratory failure); None have survived ≥ 40 days
    - ***Potter facies, oligohydramnios*** (no urine output), ***pulmonary hypoplasia*** (oligohydramnios)
    - Adrenal glands are usually normal (different embryologic origin)
    - May void in 1st 24 hours of life; however, no void after 24 hours
    - ***Lecithin-sphingomyelin ratio***: assess fetal lung maturity via ratio of pulmonary surfactants. Lecithin is main component in mature lungs.
        - * Appropriate lung maturity has a ratio > 2

Ultrasound Renal Screening

Indicated for first-degree relatives (parents, siblings, children) of patients with congenital solitary kidneys or infants with bilateral renal agenesis

- **Unilateral renal agenesis**
    - Congenital agenesis vs. involution of dysplastic kidney or multicystic dysplastic kidney

      - Agenesis: colon malpositioned into renal fossa
      - Dysplastic: colon in correct position
  - Male to female ~ 2:1; most commonly the left kidney
  - Secondary ureteric bud malformation and RET mutations
  - Males: may have absent ipsilateral body/tail of epididymis, ***vas deferens***, ampulla, seminal vesicle, and ejaculatory duct; Females: may have abnormal uterus (e.g. unicornuate uterus); both sexes have increased anomalies in other organ systems
  - ***In utero contralateral, compensatory renal hypertrophy***
  - May have increased HTN, renal insufficiency, and proteinuria

Vesicoureteral Reflux Screening

Indicated for all children with unilateral renal agenesis because ~1/3 will have reflux

SUPERNUMERARY KIDNEY

- Two distinct metanephric diverticulum form two separate ureteric buds or ureteric bud branches and each meets an independent metanephric blastema
- May have a bifid or duplex ureter
- Usually an incidental finding on imaging

CROSSED RENAL ECTOPIA

- ***Fused (90%) vs. non-fused (10%)*** to ipsilateral kidney
  - Fused: Likely one of the ureteric buds crosses over to contralateral blastema; usually fuses to the inferior pole of normal positioned kidney
- Male to female 2:1; left-to-right ectopia 2:1
- Usually the ureter inserts on original side (i.e. crossed) with normal trigone

HORSESHOE KIDNEY

- Metanephrogenic blastema fuses at inferior pole resulting in an inability to ascend superior to the inferior mesenteric artery
- Male to female 2:1
- ***Notochord***: required for proper renal positioning
- ***Sonic hedgehog gene***: criteria for renal positioning and mutation may lead to renal fusion
- Up to 1/3 have ureteropelvic junction obstruction with hydronephrosis secondary to abnormally high ureteral insertion
- Variable blood supply (e.g. multiple renal arteries)
- ***Edward's syndrome*** (trisomy 18; 20%) and ***Turner syndrome*** (45, XO; 60%) have increased incident of horseshoe kidneys
- Increased incidence of ***Wilm's tumor*** within horseshoe kidneys
- ESWL and PCNL are acceptable forms of nephrolithiasis treatment
    - PCNL access is more medial (i.e. closer to the vertebrae)
- Prior to any renal surgery, consider CT angiogram as a variable blood supply is common

Horseshoe Kidney Calyces

Calyces are directed posteriorly

ECTOPIC KIDNEY

- ~ 50% have hydronephrosis
    - Ureteral obstruction (50%)
    - Significant vesicoureteral reflux (25%)
    - Malrotation (25%)
- Increased rate of concomitant genital anomalies
- Malrotation results in an ***anterior renal pelvis*** (rather than medial)
- **Thoracic kidney**
    - Ascent of kidney through foramen of Bochdalek into the posterior mediastinum by 8th week of gestation
    - Adrenal gland is in normal position

  - Usually incidental finding on a chest x-ray

RENAL MALROTATION

- During normal embryologic renal development, the hilum is posterior with the outer concavity is anterior. As the kidney ascends it rotates ***ventromedial*** (i.e. the hilum faces the midline/aorta, and the outer concavity faces laterally/ribs)
- The kidney may over- or under-rotate

CALYCEAL DIVERTICULUM

- Outpouching of a calyx or renal pelvis lined by urothelium
  - Type 1: Upper or lower pole calyx outpouching
  - Type 2: Outpouching with thin connection directly to the renal pelvis
- Presentation variable: asymptomatic; UTI; nephrolithiasis; milk of calcium (calcium crystallization without stone formation); hematuria
- Dx: CT or MRI urogram
- Tx: periodically monitor asymptomatic patients with ultrasound; if symptomatic (UTI, calculus, etc.), proceed with diverticular ablation and stone extraction

CALYCEAL DIVERTICULUM TREATMENT

Location	Treatment Approach
Posterior	PCNL
Anterior superior pole	Ureteroscopy
Anterior mid / lower pole	Laparoscopic ablation

MEGACALYCOSIS

- Embryologic malformation of the renal papillae that results in enlarged and increased number of calyces without evidence of obstruction
- Most common in males (6:1)
- Tx: none; no evidence renal injury in long term

RENAL PSEUDOTUMOR

- Hypertrophied column of Bertin; usually between upper and middle calyces
    - High suspicion if solitary kidney with a "central tumor"
- ***Dromedary hump***
    - Solitary, renal parenchyma bulge seen laterally and usually on the left kidney; normal variant
- Dx: ***DMSA scan*** - normal or increased radioisotope uptake

| URETER |

URETEROPELVIC JUNCTION OBSTRUCTION (UPJO)

- ***Intrinsic***: area of ureter lacking peristalsis secondary to collagen deposition or poor circular musculature; may also be caused by mucosal folds
- ***Extrinsic***: aberrant, lower pole vessel crosses anteriorly to the ureter, and causes a ureteral kinking
- Associated with other congenital urologic abnormalities in infants (most commonly contralateral UPJO, renal dysplasia, multicystic kidney)
- Tx: pyeloplasty is gold standard in pediatrics (~95% success rates)
    - Endopyelotomy may also be considered in adults, if etiology is not due to a lower pole vessel
        - Up to ~ 85% success rates if no lower pole vessel, good renal function, stricture segment < 2cm, and mild-moderate hydronephrosis
    - If failed endopyelotomy, consider pyeloplasty
    - If failed pyeloplasty, consider endopyelotomy
    - If failed pyeloplasty with long stricture, consider ureterocalicostomy

Dietl's Crisis

Patients with UPJO have acute renal colic secondary to diuresis (e.g. alcohol ingestion)

BIFID URETER/ URETER FISSUS

- Two ureters at the renal pelvis (i.e. ***duplex kidney***) with a solitary, shared ureteral orifice
- Partial division of the ureteric bud, prior to contact with metanephrogenic blastema
- Triple and quadruple ureters have also been reported

DUPLICATED URETER

- Two ureters at the renal pelvis (i.e. ***duplex kidney***) with two completely separate ureters that have their own ureteral orifice
- Complete division of ureteric bud prior contact with metanephrogenic blastema
- **Weigert-Meyer Rule**
    - Upper pole associated with ureterocele and ectopic
    - Lower pole associated with vesicoureteral reflux and UPJO
- MAG3 scan: determine function of each renal unit/segment
    - If symptomatic and minimal function: partial nephrectomy
    - If symptomatic or asymptomatic and functional: correct any obstruction
    - If asymptomatic and minimal function: observation

Weigert-Meyer Rule

Upper pole: ureteral orifice is inferior / medial; ureterocele

Lower pole: ureteral orifice is superior / lateral; VUR

ECTOPIC URETER

- Ureteral orifice is not located within the bladder trigone
- Females: anywhere from bladder neck to the rectum
  - Will not insert directly into a Mullerian structure, rather into associated Wolffian duct remnants
  - ***Continuous incontinence*** if distal to sphincter/bladder neck (DDx: vesicovaginal fistula, urethrovaginal fistula, patent-stove pipe urethra, epispadias)
- Males: anywhere from the bladder neck to the proximal extent of the external sphincter, particularly into the Wolffian structures
  - Males never present with incontinence because the ectopic ureter always inserts proximal to the external sphincter
- Tx: ureteral re-implant
  - Note: do not separate duplicated or bifid ureters, as this may injury ureteral vasculature

URETEROCELE

- Cystic dilation seen in the distal, ectopic ureter secondary to persistent ***Chwalla's membrane***
- May be intra- or extra- vesical; obstructive or non-obstructive
- ***Cecoureterocele***: a portion of the ureterocele extends into the urethra
  - Difficult to diagnose and treat
- ***VCUG*** is required prior surgical intervention
- IVP or CT scan: ***cobra-head appearance*** (contrast within the ureterocele and not contrast surrounding it)
- Bladder ultrasound: study of choice in pediatrics
  - Will have hydronephrosis (upper pole if duplex system)
  - DDx: hydroureter without ureterocele
- ***Ureterocele prolapse*** through the urethra
  - DDx: urethral prolapse (circumferential); sarcoma botryoides (lobulated and vaginal origin)
- Tx options: transurethral incision; excision of ureterocele with ureteral re-implant; marsupialization; upper pole nephrectomy if non-functioning; ureteroureterostomy

  - Consider prophylactic antibiotics until a definitive treatment is completed

RETROCAVAL URETER

See Urologic Radiology Chapter

MEGAURETER

- Non-specific term for a severely dilated ureter (> 7-8 mm)
- **Primary:** intrinsic ureteral abnormality leading to a lack of peristalsis
  - Tx: majority resolve without intervention in time; however, ureteral re-implantation may be necessary
  - Note: if improved, but not completely resolved, check a renal ultrasound at puberty to evaluate for potential silent worsening
  - Re-implant: will need distal remodeling to allow a ***5:1 tunnel length-to-diameter ratio*** to prevent reflux
    - Plication: moderate hydronephrosis
    - Excision tapering: severe hydronephrosis
    - Divide the medial umbilical ligament (i.e. obliterated umbilical artery) as it loops laterally to posterior the ureter. This eliminates possible ureteral obstruction.
- **Secondary:** severe vesicoureteral reflux; bladder outlet obstruction; neurogenic bladder; polyuria
  - Tx: address underlying disease process
- Antibiotic prophylaxis is recommended until resolved

| BLADDER |

URACHAL ANOMALY DESCRIPTION

Urachal Anomaly	Bladder End	Mid Portion	Umbilical end	Incidence
Normal	Completely obliterated = ***median umbilical ligament***			
Patent urachus (urachal fistula)	Patent	Patent	Patent	50%
Diverticulum	Patent	Obliterated	Obliterated	5%
Cyst	Obliterated	Patent	Obliterated	30%
Sinus*	Obliterated	Obliterated	Patent	15%

** Rule out Meckel's diverticulum (persistent omphalomesenteric duct)*

- Some infants will not urinate in the first 24 hours, which is normal variant.

URACHAL ANOMALIES

- Dx: fistulogram, sonogram, VCUG, or ultrasound
- Patent urachus: Secondary to congenital bladder outlet obstruction (e.g. posterior urethral valves); Umbilical urine drainage
    - If infected/abscess, antibiotic treatment prior excision with bladder cuff
- Urachal diverticulum: located at the bladder dome
- Urachal cyst: may intermittently drain via bladder or umbilicus
    - If infected/abscess, likely staphylococcus aureus; percutaneous drainage with antibiotics followed by complete excision

Urachal Adenocarcinoma

Located at bladder dome

Tx: partial cystectomy

MEGACYSTIS

- Non-specific distended, thin fetal bladder secondary to either anatomic or functional obstruction
- Megacystis microcolon intestinal hypoperistalsis syndrome (MMIH or Berdon syndrome) is rare syndrome that includes megacystis
    - Mistaken for prune belly syndrome

BLADDER AGENESIS

- Likely defect of upper anterior cloaca
- Not compatible with life unless ectopic ureters

BLADDER DUPLICATION

- Complete vs. incomplete; sagittal vs. coronal arrangement; common/shared vs. duplicated urethra
    - Most common is complete / sagittal
- Vast majority has concomitant external genital anomalies, and high incidence of lower gastrointestinal anomalies

BLADDER DIVERTICULUM

- Bladder mucosal herniation through detrusor muscle
- Dx: VCUG, IVP, cystogram, or CT urogram
- **Primary**: congenital defect
    - Seen in Ehlers-Danlos, Marfan syndrome, Menkes syndrome, William Elfin-facies
    - Tx: conservative; consider excision if concomitant vesicoureteral reflux

- **Secondary**: bladder outlet obstruction resulting in elevated bladder pressures
  - o Tx: address bladder outlet obstruction; excise diverticulum if symptomatic

Hutch Diverticulum

Paraureteral orifice diverticulum

BLADDER EXSTROPHY-EPISPADIAS COMPLEX

- Urinary bladder is everted through the abdominal wall
- Associated with pelvic bone abnormalities that leads to pelvic widening and distal rectus muscle divergence; epispadias
- Etiology: ***premature cloacal membrane rupture*** leading to infraumbilical anomalies from deficient mesenchyme caudal migration between the ectodermal and endodermal layers
- Dx: antenatal ultrasound: low-set umbilical cord, lower abdominal wall mass, bladder not seen in abdomen, abnormal genitalia
- Variants: classic bladder exstrophy, cloacal exstrophy, epispadias, covered exstrophy, duplicate exstrophy, superior vesical fissure
- ***Classic Bladder Exstrophy*** (most common variant)
  - o The rectus muscles divide distally and widen the pelvic bones, which creates a triangular fascial defect that allows eversion of bladder with visible bladder mucosa through the abdominal wall.
  - o High incidence of indirect hernia secondary to widened pelvis
  - o These children are generally healthy
  - o Tx: immediate protect mucosa with saline wrap; first day of life closure without osteotomies if possible; primary vs. delayed epispadias repair
- ***Cloacal Exstrophy*** (rare)
  - o Non-tubularized cecum and hemi-bladder are open and everted through the abdominal midline

  - *o* The split penis is completely separated into corpora cavernosal and respective hemi-glans
  - *o* Numerous associated anomalies, including renal anomalies and short gut syndrome
  - *o* These children are usually very ill
  - *o* Tx: immediate closure and genital repair
- ***Epispadias*** (extremely rare)
  - *o* Incomplete urethral tubularization resulting in dorsal penile urethral drainage in boys, while females have urethral drainage usually between the clitoris and labia
  - *o* Usually bifid penis with chordee or bifid clitoris
  - *o* Tx: if isolated: repair at 6 months of age
    - * If complex: consider primary vs. delayed repair

| PROSTATE |

PROSTATIC UTRICLE

- Represents vestigial, distal 1/3 of vagina secondary to decreased or lack of androgen
- Most commonly associated with proximal hypospadias
- Pelvic ultrasound: cystic appearing structure found behind the bladder

| PENILE ANOMALIES |

GLANULAR ADHESIONS / SYNECHIA

- Circumcised: irritation from suprapubic fat pad or diaper
- Uncircumcised: congenital; majority will breakdown by adolescence

APHALLIA

- Penis is absent
- Genital tubercle developmental abnormality
- Urethra drains near or within the anorectal region
- Associated with multiple other congenital anomalies

DIPHALLIA

- Penile duplication
- Variable phenotype with other anomalies
- Screen with renal ultrasound and VCUG

BURIED (HIDDEN OR CONCEALED) PENIS

- Penis obscured by suprapubic fat pad
- Congenital: inelastic Dartos fascia
- Acquired: obesity or post-circumcision circumferential scarring (trapped penis)
- DDx: micropenis (buried penis has normal penile stretch length, while the micropenis is < 2.5 age-adjusted, standard deviations from the mean
- Will have a normal penile stretch length

WEBBED PENIS (PENOSCROTAL FUSION)

- Scrotal tissue extends up onto the ventral aspect of the penis
- Tx: scrotoplasty prn

MICROPENIS

- Penile stretch length < 1.9 cm (< 2.5 age-adjusted standard deviations from the mean)
- Fetal hypogonadism after initial growth
    - Most commonly ***hypogonadotropic hypogonadism***
- Lab: karyotype, serum testosterone (pre- and post-hCG stimulation), LH, FSH, BMP, thyroid panel, cortisol
- Tx: Testosterone trial x 3 months; if penile growth, continue until within reference range

CHORDEE

- Congenital, ventral penile curvature
- Associated with hypospadias

CORPORAL BODY DISPROPORTION

- Different corporal body lengths
- Results in lateral curvature

PENILE TORSION

- Penile rotation; usually counterclockwise
- DDx: wandering raphe (penile raphe off midline with normal penile orientation)
- ***Mild: < 60° rotation***
- ***Moderate: 60-90° rotation***
- ***Severe: > 90° rotation***
- Tx: mild: cosmetic correction (if desired)
    - Moderate/severe torsion: functional correction with lysis of dysgenic fibrous bands near the penile base

MEDIAN RAPHE EPIDERMAL CYST

- Commonly found along raphe of penis, scrotum, and/or perineum
- If symptomatic, excise the cysts

| URETHRA |

MEATAL STENOSIS

- Post-circumcision as an infant; related to diaper irritation
- Narrow, split stream
- In adults, may be secondary to urethral manipulation (e.g. cystoscopy)
- Tx: meatoplasty or meatotomy

URETHRAL DUPLICATION

- Variable presentation; vast majority are in the sagittal plane
- Dorsal urethra is usually the anomalous organ
- Effman classification is used to categorize
- Most common: sagittal duplication with two separate meatuses and an ability to void through both simultaneously
- DDx: hypospadias (glanular dimple is not patent)
- Dx: VCUG, RUG, and cystoscopy
- Tx: surgical (approach depends on anatomic anomaly)

| SCROTUM |

PENOSCROTAL TRANSPOSITION

- Scrotum superior and penis inferior
- Associated with ***proximal hypospadias*** and other genitourinary anomalies
- Screen with RUS and VCUG
- Tx: hypospadias repair with scrotoplasty

BIFED SCROTUM

- The hemiscrotum are independent without septal attachment
- Incomplete labioscrotal fold fusion

SCROTAL HYPOPLASIA

- Hemiscrotal or complete scrotal underdevelopment
- Common in undescended testicles
- NOTE: if complete scrotal development without hypoplasia, a testicle did descend into the scrotum at some point during development

SCROTOSCHISIS

- Extrusion of a testicle through a congenital scrotal wall defect

| NEONATAL ANOMALIES |

- ***Sacral agenesis***: associated with maternal insulin dependent diabetes mellitus
- ***Renal vein thrombosis***: associated with maternal hypertension

CHAPTER 4: UROLOGIC RADIOLOGY

This chapter is designated to highlight the radiologic findings in specific urologic disorders. Please refer to subsequent chapters for more detailed information and treatment of these disorders.

RENAL ULTRASOUND

- Anatomic study, not a functional study
- **Echogenicity**
    - Hyperechoic: brighter / white
    - Hypoechoic: darker / black
    - Isoechoic: similar echogenicty to a comparable area
    - Healthy liver is point of reference for echogenicity
- Gerota's fascia and perinephric fat: hyperechoic area surrounding kidney
- Renal cortex: homogenous, grey area in renal periphery
- Renal sinus: hyperechoic central area
- Hydronephrosis: hypoechoic enlargement of renal pelvic and calyces
- **Resistive Index (Ri)**
    - RI = (systolic – diastolic) / systolic
    - Normal RI = 0.6
    - ***Renal obstruction: RI > 0.7*** or RI difference between kidneys > 0.1
    - Elevated RI: transplant rejection, obstruction, ATN, pyelonephritis, severe hypotension, or an acute vascular event (e.g. renal vein thrombosis).
    - If ***renal artery stenosis***, there is decreased peak systolic flow

velocity while the peak diastolic increases, resulting in ***decreased RI.***

COMPUTED TOMOGRAPHY (CT) SCAN

- ***Unenhanced phase***: best phase for renal calculi, renal mass baseline for amount of enhancement
    - Anatomic study, not a functional study

ENHANCEMENT (I.E. IV CONTRAST) PHASES

1. ***Corticomedullary phase***: renal vascular disease, aneurysm, arteriovenous malformation or fistula
2. ***Nephrographic phase***: best phase for renal mass
3. ***Excretory phase***: collecting system

- Function and anatomic study

Renal Mass CT Scan Phase Requirements

(1) Unenhanced (2) Corticomedullary (3) Nephrographic

- **Contrast Induced Nephropathy**
    - Etiology is unclear; however, likely toxic effect on proximal tubules
    - Acute tubular necrosis (ATN): ***24-72 hours after contrast*** administration
    - Prevent with adequate hydration – consider IV fluids before and after IV contrast administration; N-acetylcysteine is an antioxidant which may be beneficial
- All child-bearing aged women need a negative pregnancy test prior to CT scan

CT SCAN HOUNSFIELD UNITS

Substance	HU Value
Air	- 1,000
Fat	- 20 to -100
Water	0
Muscle	40
Acute bleed*	30-45
Clotted blood*	> 60
Bone	400 to 1,200
Metal	> 1,500

** Acute blood has high protein count leading to increased HU; clotted blood has an even higher HU because of an increased hemoglobin concentration*

INTRAVENOUS PYELOGRAM (IVP)

- Intravenous contrast given and followed by multi-plane x-rays and tomograms
- Functional and anatomic study
- Less radiation exposure than CT scan; however, less anatomic information

MAGNETIC RESONANCE IMAGING

- A magnet is used to align protons, and then a radio frequency is administered. This creates an electromagnetic field and alters alignment of the protons. A receiver coil measures the changes and a computer image is generated.
- ***T1-weighted scan***: water is dark and fat is bright
- ***T2-weighted scan***: water is bright and fat is dark
    - o Look at cerebral spinal fluid, and it will be white/bright

MRI T2 Mnemonic

H2O (on T2) is a bright idea to make fat go away (fat is dark); T1 is opposite

- **Nephrogenic Systemic Fibrosis**
    - Etiology: inability of renal clearance of ***Gadolinium*** used in enhanced ***MRI***
    - Skin: fibrosis and hardened skin, plaques, pigmentation
    - Joints: contractures
    - Internal organs: systemic fibrosis
    - Highest risk in patients with ***GFR < 30***
- ***MRI non-compatible devices***
    - Pacemaker
    - Deep brain stimulators
    - Metallic ocular foreign body
- ***Urologic devices and MRI***
    - Interstim: head-only MRI's may be conducted
    - Artificial urinary sphincter: MRI safe
    - Penile prosthesis
        - AMS 700 series, Ambicor, Dura II: MRI safe
        - Titan series, Spectra, Genesis: MRI conditional
    - Ureteral stents
        - Routine (majority) ureteral stents: MRI safe
        - Cook Black Silicone Filiform and Resonance: MRI conditional
    - Brachytherapy: MRI conditional
    - See MRIsafety.com for further details

NUCLEAR STUDIES

- All child-bearing aged women need a negative pregnancy test prior to nuclear studies

BONE SCINTIGRAPHY (SCAN)

- A radioisotope, usually ***Technetium-99m***-methylene diphosphonate is administered intravenously, and after 3-4 hours a gamma camera detects the emission of radiation and its subsequent location
- "Hot spots" may be seen in metastatic lesions and trauma (even in several years old traumatic injuries)
- Common urologic indications: metastatic prostate and renal carcinoma

Bone Scan Lesions

Prostate Cancer: majority are osteoblastic lesions

Renal Cancer: majority are osteolytic lesions

- If incidental renal isotope retention (i.e. obstruction), perform a CT urogram or a MAG3 renal scan
- ***"Super Scan"***: diffuse skeletal absorption of Technetium-99 without uptake (i.e. drainage) seen in the kidneys/bladder
  - May be seen with diffuse metastatic disease, such as advanced metastatic prostate cancer
- Do not confuse with a ***Dual Energy X-ray Absorptiometry (DEXA) scan***, which is used to determine bone mineral density (e.g. osteoporosis in patients on androgen deprivation therapy)

RADIONUCLIDE RENAL SCANS

- **DMSA (DiMercaptoSuccinic Acid)**
  - Binds renal proximal tubules
  - Use: identify renal scar; confirm renal pseudotumor
    - Increased density = pseudotumor
    - Decreased density = cyst or solid tumor

DMSA Mnemonic

DMSA, this Meat (Cortex) of kidney

- **MAG3 (MercaptoAcetyltriGlycine)**
  - Excreted by renal proximal tubules
  - Use: determine renal function; identify obstruction
  - Usually with Lasix washout; also a Foley catheter is encouraged to decreased false results.

MAG3 HALF-LIFE INTERPRETATION

Half-life (minutes)	Interpretation
< 10	Normal
10-20	Equivocal
> 20	Obstruction*

** False positives: severe renal pelvis dilation, renal insufficiency*

- **DTPA (DiethyleneTriaminePentaacetic Acid)**
  - Cleared by GFR, not excreted
    - * Do not use if low GFR; use MAG3 instead
  - Uses: determine GFR and renal function, identify obstruction

VOIDING CYSTOURETHROGRAM (VCUG)

- Bladder instillation of contrast via a urethral catheter, and subsequent fluoroscopic imaging
- Modality of choice for ***vesicoureteral reflux***

VESICOURETERAL REFLUX GRADING

Grade	Reflux Description
1	Ureteral reflux only
2	Ureteral ***and*** renal pelvis reflux ***without*** dilation
3	Ureteral ***and*** renal pelvis reflux with ***mild*** dilation
4	Ureteral ***and*** renal pelvis reflux with ***moderate*** dilation
5	Ureteral ***and*** renal pelvis reflux with ***severe*** dilation and tortuosity

| ADRENAL |

BENIGN ADRENAL ADENOMA

- CT scan adrenal mass with ***Hounsfield units < 18***
- CT scan contrast ***washout > 60% at 15 minutes***
- MRI scan: chemical shift imaging; "out of phase" imaging (***drop in signal intensity > 20%***)

PHEOCHROMOCYTOMA

- Adrenal adenoma on CT scan, need functional studies
- MRI has ***high signal intensity on T2***-weighted images
- ***MIBG (metaiodobenzylguanidine) scan*** for metastatic pheochromocytoma or identification of unknown location of pheochromocytoma
  - *o* Many medications interfere with test including: opioids, tramadol, cocaine, tricyclic antidepressants, sympathomimetics, antihypertensives, ACE-inhibitors, antipsychotics.

ADRENOCORTICAL CARCINOMA

- Tend to be larger adrenal masses and majority are functional
- Venous tumor extension is common (may need MRI to better characterize)

- Adrenal mass with calcification is a highly suspicious finding
- Adrenal cysts may be malignant

Incidence of Malignant Adrenal Incidentaloma

< 4 cm: 2% 4-6 cm: 6% > 6 cm: 25%

MYELOLIPOMA

- CT scan: fatty tumor (***negative Hounsfield units***)
- MRI scan: ***fat*** - high signal intensity on T1 weighted scans; ***bone marrow elements*** – low signal intensity on T1 and moderate signal on T2 weighted scans

| RENAL |

RENAL CYSTS

- Common, renal, ***cortical*** lesions; and majority are benign, simple cysts
- Most commonly found in ***adults***
- Bosniak scale via CT scan determines follow up and management

BOSNIAK SCALE AND MANAGEMENT

Bosniak Classification	**CT findings ***	**Risk of Malignancy**	**Management**
1	Simple cyst (simple fluid HU 0-20), thin wall; No septa or calcifications	~ 0%	Only if symptomatic, otherwise no surveillance
2	Thin septa, fine calcification, < 3cm; **hyperdense**	< 3%	Only if symptomatic, otherwise no surveillance
2F	Endophytic, > 3cm, multiple thin septations, calcifications	5-10%	***Periodic surveillance (CT, MRI, or renal ultrasound)***
3	Thick or irregular septa or walls; increased calcifications, may have enhancement	~ 50%	***Surgical excision***
4	Thick walls or nodular areas; marked heterogeneity; contain enhancement	75-90%	***Surgical excision***

** Category 1-2F lack contrast enhancement; while 3-4 have contrast enhancement*

POLYCYSTIC KIDNEY DISEASE

- Innumerable, bilateral, renal cortical cysts and hepatic cysts
- Associated with ***Berry aneurysms*** on brain imaging
- Autosomal dominant: adults; autosomal recessive: pediatrics
- CT scan: imaging of choice, and diagnostic

NEPHRONOPHTHISIS

- Renal, ***medullary*** cysts formed at the corticomedullary junction
- Most commonly found in ***pediatrics***

NEPHROLITHIASIS

- Renal derived calcifications (i.e. calculi) within the urinary collecting system
- CT scan is the most sensitive imaging study for detection of nephrolithiasis (> 95%)
  - CT scans are unable to visualize Indinavir calculi (protease inhibitor for HIV)
- MRI scan does not visualize calculi well
- Renal ultrasound may be used to detect renal calculi and possibly proximal ureteral calculi
- KUB x-ray may detect radiopaque calculi; however, may be limited by bone structures and intestinal gas patterns
- **Radiopaque**: calcium oxalate (both monohydrate and dehydrate), magnesium ammonium phosphate (struvite), calcium phosphate, and cystine (poorly opaque)
- **Radiolucent**: uric acid, xanthine, Indinavir, ammonium urate, matrix

NEPHROCALCINOSIS

- Renal derived calcifications found in the ***renal parenchyma***
- Etiology: medullary sponge kidney, hyperparathyroidism, distal RTA (type 1), Tuberculosis, papillary necrosis, hyperoxaluria

RENAL PSEUDOTUMORS

- DMSA scan is helpful to distinguish renal pseudotumors
- **Dromedary Hump:** Normal renal contour variant with a single bulge on the lateral renal border
- **Hypertrophied Column of Bertin**: normal variant with enlargement of the cortex between the renal pyramids
- **Persistent Fetal Lobulation**: incomplete renal lobule fusion during development results in contour indentations in between the renal pyramids

RENAL CELL CARCINOMA

- All ***enhancing (≥ 20 HU increase)*** renal parenchymal lesions, with positive Hounsfield Units (i.e. no fat) are considered carcinoma until proven otherwise
- ***MRI scan*** is helpful for delineation of ***renal vein and inferior vena cava involvement / staging***
  - MRI T2 weighted signal intensity
    - Hyperintense: clear cell RCC
    - Hypointense: papillary RCC
- Women: ***mammogram*** – rule out breast cancer
- Neurologic findings: ***CT brain***
- ***Chest x-ray*** all patients; CT scan chest if inconclusive x-ray
- ***Bone scan*** if elevated alkaline phosphatase, bone pain, or pathologic fracture

ONCOCYTOMA

- Enhanced imaging or angiography may show a ***spoke wheel pattern***

ANGIOMYOLIPOMA

- ***Negative Hounsfield Units on CT scan (i.e. fat) in a renal mass***
- If calcification is present, consider it a carcinoma
- Be aware of epithelioid variant, which has a paucity of fat
- On ultrasound, the AML is ***echogenic mass*** (highly suggestive of AML) and produces a ***speed propagation artifact*** (sound waves slow in fat, which makes posterior objects appear further in the distant)
  - Echogenic mass with no shadowing is pathognomonic

MEDULLARY SPONGE KIDNEY

- Benign congenital disorder with multiple cysts in ***collecting ducts***
- Nephrocalcinosis is present
- ***Paint brush-like calyces***

PYELONEPHRITIS

- CT scan with contrast: focal wedge defect with reduced enhancement, including the rim (rim is enhanced with renal infarcts)
- **Emphysematous pyelonephritis**: gas within the renal parenchyma
- **Emphysematous pyelitis**: gas within the renal collecting system

XANTHOGRANULOMATOUS PYELONEPHRITIS (XGP)

- CT scan: ***Bear's paw sign*** (decompressed renal pelvis with dilated calyces) and staghorn calculus
- Contrast study or renal nuclear scan: poor renal function
- May be confused with RCC

GENITOURINARY TUBERCULOSIS

- CT urogram is study of choice
- Renal
  - ***Moth-eaten calyx***: calyceal erosion and necrosis
  - ***Infundibular stricture*** and renal parenchymal calcifications
  - ***Putty kidney***: caseous, necrotic, radiopaque material seen in end-stage renal tuberculosis
- Ureter
  - ***Sawtooth ureter***: mucosal irregularities / beading
  - Strictures most common distally
- Bladder
  - ***Thimble bladder***: thickening of bladder wall with reduced capacity

RENAL INFARCT

- CT scan with contrast: focal wedge defect with reduced enhancement; however, the rim of the cortex (***cortical rim sign***) continues to enhance from collateral blood supply.
  - Cortical rim sign is present in ~50% of cases; and best seen several hours to days after the infarct

RENAL DISEASE

- ***Diffuse increased echogenicity in bilateral renal parenchyma***
- Usually loss of corticomedullary differentiation and renal atrophy (< 9 cm is ominous for end-stage kidneys)
    - Best measured with renal ultrasound

| URETER |

URETEROLITHIASIS

- CT scan without contrast has become imaging study of choice
- ***Soft-tissue rim sign***: adjacent, surrounding soft tissue associated with ureteral edema from an impacted ureterolithiasis
- ***Comet tail sign***: adjacent, irregular tapering of soft tissue mass that is non-calcified vein associated with ***phleboliths***

DUPLICATED URETERS

- ***Weigert-Meyer Rule***: upper pole inserts the bladder inferior/medial and the lower pole inserts the bladder superior/lateral
- ***Drooping lily sign***: hydronephrotic, nonfunctioning upper pole displaces the opacified, functioning lower pole inferior to appear like a drooping lily
- ***Ectopic ureter***: if unable to identify on ultrasound, MRI is best imaging modality to identify the ectopic insertion
    - Most commonly associated with ***upper pole moiety***
    - if insertion is beyond the external sphincter, continuous urinary leakage may be present (rule out fistula)

RETROCAVAL URETER (CIRCUMCAVAL URETER; PREURETERAL VENA CAVA)

- The right ureter courses posterior and medial to the inferior vena cava (IVC), and then crosses anterior to the IVC heading laterally towards the common iliac bifurcation
- Etiology: ***persistent right subcardinal vein*** during ureteral

development

- Sx: flank pain, UTI, asymptomatic
- Tx: ureteroureterostomy with removal of retrocaval portion because it is usually aperistaltic

RETROPERITONEAL FIBROSIS (ORMOND'S DISEASE)

- ***Medial deviation of the ureters*** (other etiologies such as neoplasm, aneurysm, idiopathic, retroperitoneal vascular surgery, etc. may cause medial deviation)

URETERAL TUMOR

- ***Goblet sign***: Ureteral dilation just distal to the ureteral tumor (ureteral calculi cause distal ureteral spasm)

PREGNANCY ASSOCIATED HYDROURETER

- Right > left ureter
- Most prominent at 22-24 weeks; seen on ultrasound
- Etiology: (1) gravid uterine compression (2) elevate progesterone relaxes smooth muscle

URETEROCELE

- IVP or CT with contrast/delay show the thin wall of the ureterocele separating ureteral and bladder contrast (***cobra-head deformity***)
- May also be seen on ultrasound that appears as a ***cyst within a cyst***
- Renal imaging will likely confirm a duplicated collecting system
    - o Ureterocele is associated with the ***upper moiety***

| URINARY BLADDER |

BLADDER RUPTURE

- CT cystogram or plain cystogram
    - o ***Need a minimum 350cc of contrast instilled into the bladder***

for adequate study

  - Post-drainage films are imperative to evaluate for posterior rupture

Bladder Imaging

Allowing the bladder to fill in an antegrade fashion with contrast from a CT with contrast or an IVP is not an acceptable substitution for a cystogram

- **Intraperitoneal rupture**: contrast outlines the small bowel
- **Extraperitoneal (retroperitoneal) rupture**: contrast located posterior to the bladder

BLADDER ULTRASOUND

- ***Normal bladder wall thickness is ≤ 5mm***
  - If abnormal in pediatric patients, a VCUG is needed to rule out obstruction (e.g. posterior ureteral valves)
- In ***prenatal*** patients, non-visualization of the bladder at multiple separate times indicate the possibility of poor renal function with oligohydramnios, cloacal exstrophy, bladder exstrophy, or persistent cloaca
  - Bladder exstrophy: absent bladder, anterior abdominal mass, and low set umbilicus

PELVIC LIPOMATOSIS

- CT scan: excessive pelvic fat
- ***Pear-shaped bladder***: inverted teardrop-shaped bladder
  - Other etiologies: pelvic hematoma, pelvic fluid, psoas muscle hypertrophy, lymphadenopathy, bilateral iliac arterial aneurysms
- Most common in middle aged, African-American males; often presents with lower urinary tract symptoms (LUTS)

BLADDER HERNIAS

- ~1-3% of inguinal hernias have associated bladder herniation
- Inguinal canals (MC in men) and femoral canals (MC in females)
- Cystogram is imaging technique of choice

EMPHYSEMATOUS CYSTITIS

- Gas forming bacteria within the bladder wall seen on CT scan or x-ray
- Do not confuse with intraluminal bladder air; usually from urinary tract manipulation

SCHISTOSOMIASIS CYSTITIS

- Plain x-ray shows a thin, calcified bladder wall; may extend up the ureter
    - Etiology: calcified Schistosoma ova

VESICOENTERIC FISTULA

- ***CT scan with oral contrast*** (no IV contrast avoid confusion of bladder contrast)
- ***Bourne test***: 1st urine post-barium enema study is spun down and x-rayed
    - If radiopaque material is present, positive vesicoenteric fistula

HUTCH DIVERTICULUM

- Ureterovesical junction diverticulum
- Seen on VCUG or cystogram; and may have associated vesicoureteral reflux
- Men > Women

| PROSTATE |

TRANSRECTAL ULTRASOUND (TRUS)

- For the evaluation of prostate cancer, TRUS alone is not indicated, and requires concurrent prostate biopsy
    - Lesions suspicious for prostate cancer tend to be ***hypoechoic***
- Frequency reduction: increases depth of view; however, decreases resolution
- Gain reduction: decreases resolution

Prostate Volume Formula

0.524 x height x width x length

(Largest measurement of each category used)

PROSTATE CANCER AND MRI SCAN

- Prostate cancer: low signal intensity on T1 and T2 weighted images
- Prostate biopsy hemorrhage: high T1 and low T2 signal intensity
- Up to ~ 80% accuracy for prostate cancer staging

INDIUM (^{111}IN) CAPROMAB PENDETIDE (PROSTASCINT®)

- Radiolabeled monoclonal antibodies to PSA are given intravenously
- A SPECT (single photon emission computed tomography) is obtained at baseline and in 4-5 days to allow intestinal / cardiovascular washout.
- Highlights sites of soft-tissue prostate cancer metastasis

PROSTATE ABSCESS

- May be detected on TRUS, CT scan, MRI scan
- Usually located in the central or transitional zones of the prostate
- TRUS (image of choice): hypoechoic or anechoic lesions
  - May drain abscess at time of diagnosis
  - If patient cannot tolerate TRUS, proceed with CT or MRI scan

| PENIS |

PENILE DOPPLER ULTRASOUND

- Doppler ultrasound of cavernosal artery (deep penile) after intracavernosal injection of prostaglandin E1

- Use to predict response to phosphodiesterase type 5 (PDE5) inhibitors in patients with erectile dysfunction
- ***Peak cavernosal artery systolic velocity ≥ 35 cm/second*** is normal during an erection
    - o > 25 cm/sec peak cavernosal artery systolic flow = requirement for an erection to occur
    - o < 25 cm/sec = severe arterial disease
- ***Peak cavernosal artery end-diastolic velocity < 5cm/sec*** is normal during an erection
    - o > 5 cm/second = ***Venous leak*** (penile veno-occlusive disease)

PENILE FRACTURE

- Imaging is usually unnecessary
- MRI and ultrasound can determine if ***tunica albuginea*** is intact or ruptured

| URETHRA |

RETROGRADE URETHROGRAM (RUG)

- X-ray imaging of retrograde instillation of contrast within the urethra; anterior-posterior and oblique views are required
- Indications: urethral trauma (***blood at the meatus***), stricture, evaluate a urethroplasty
    - o Medial inferior rami and pubic diastasis are predictive of urethral injuries = obtain RUG

Urethra Stricture Imaging

Ultrasound offers the most accurate measurement of anterior urethral strictures, and only modality to assess for spongiofibrosis

VOIDING CYSTOURETHROGRAM

- X-ray images of retrograde instillation of contrast into the bladder and subsequent voiding
    - ***Pediatric bladder capacity in mL = (age + 2) x 30***
- Indications: pediatric febrile UTI, prenatal hydronephrosis, voiding abnormalities, posterior urethral valves, vesicoureteral reflux, bladder neck contracture

URETHRAL DIVERTICULUM

- Retrograde urethrogram, voiding cystourethrogram, MRI, and even ultrasound may be used to detect a urethral diverticulum
- Symptoms: ***The 3 D's = Dysuria, Dyspareunia, Dribbling***
- Pelvic MRI scan is imaging of choice

| TESTICLE |

TESTICULAR TUMORS

- Testicular ultrasound is the diagnostic choice of imaging
- ***Testicular cancer*** are ***hypoechoic*** lesions
    - Seminoma are more homogenous
    - Lymphoma tend to have multifocal hypoechoic lesions
- ***Testicular microlithiasis***
    - ≥ 5 microcalcifications within the testicle
    - Commonly seen in patients diagnosed with testicular cancer; however, microlithiasis without a testicular mass does not have an increased risk of testicular cancer
- Usually ***extra-testicular masses*** are benign
    - Lipomas (spermatic cord)
    - Adenomatoid tumor (epididymis or testicular tunica vaginalis)

Absent Vas Deferens

Renal ultrasound to rule out absent ipsilateral kidney

EPIDIDYMITIS / ORCHITIS

- Enlarged epididymis / orchitis with decreased echogenicity; commonly with a reactive hydrocele
- Hypervascularity seen on Doppler ultrasound

HYDROCELE

- Ultrasound: anechoic (black) area surrounding a testicle; if complex, may have septations or internal echos

VARICOCELE

- Venous dilation / flow of the pampiniform plexus
- Most common: left > right secondary to insertion into the left renal vein and increased length
    - Right varicocele: indication for CT abdomen/pelvis to rule out malignancy

VARICOCELE GRADING

Grade	Description
Subclinical	Detected on ultrasound, but ***not*** on clinical exam
1	Palpated only with valsalva
2	Palpated without valsalva
3	Visible without palpation

TESTICULAR TORSION

- Color Doppler Ultrasound is test of choice
    - Heterogeneous, hypoechoic testicle; may have a hydrocele
- ***Ring of Fire***: decreased blood flow with surrounding, circumferential hypervascularity

| RADIATION SAFETY |

RADIATION EXPOSURE

- Radiation scatter of the primary beam from the patient is main source of physician radiation exposure
- **A.L.A.R.A.** = As Low As Reasonably Achievable
    - Minimize radiation exposure
- Major Principles
    - ***Time***: reduce exposure time
    - ***Distance***: a doubling of distance from radiation source decreases exposure by a factor of 4
    - ***Shielding***: lead shields, aprons, thyroid shields, and eye glass lenses reduces radiation exposure
- Permissible annual dose for occupational exposure
    - Whole body: 5 rems
    - Ocular lens: 15 rems

ABSORPTION DOSE

- rad (conventional unit)
- gray or Gy (standard international unit)
- Conversion: 100 rad = 1 Gy

- **Biologic risk of radiation exposure**
    - rem (conventional unit)
    - sievert or Sv (standard international unit)
    - Conversion: 100 rem = 1 Sv

- KUB stomach exposure = 0.25 mSv
- CT stomach exposure = ≥ 12.5 mSv (50+ times greater than a KUB)

CHAPTER 5: ADRENAL TUMORS

| ADRENAL INCIDENTALOMA |

- Incidentaloma: an adrenal mass, usually > 1cm, found incidentally on abdominal imaging
- All solid adrenal masses require functional screening
- **Nonfunctioning adenoma (80%)**
  - If CT scan ***Hounsfield units < 18*** or ***CT contrast washout > 60% at 15*** minutes, then it is considered a ***benign adrenal adenoma;*** however, it may be functional
- **Functioning adenoma (10%)**
  - Cushing's Syndrome
  - Pheochromocytoma
  - Conn's Syndrome (Aldosteronoma)
- **Malignancy (10%)**
  - Metastatic lesion (majority)
    - If known primary cancer, ~ 50% of all solid adrenal masses will be metastatic disease
  - Adrenal cortical carcinoma
    - Majority are functional!

ADRENAL INCIDENTALOMA MALIGNANCY

Tumor Size	Risk of Malignancy
< 4 cm	2%
4-6 cm	6%
> 6 cm	25%

** NOTE: CT scan underestimates tumor size up to 1cm, so remove all > 5 cm!*

| PRIMARY HYPERALDOSTERONISM / CONN'S SYNDROME |

- Aldosterone resorbs sodium, and excretes hydrogen and potassium in the distal renal tubule
- Dx: refractory HTN, muscle cramping/weakness, profound hypokalemia if placed on diuretics
- DDx: Functioning adenoma vs. bilateral adrenal hyperplasia
    - Secondary hyperaldosteronism: consider reninoma, renovascular HTN
- ***Benign, aldosterone-secreting adenomas are < 3 cm*** (malignant are usually > 3 cm)
- Lab: ***hypokalemia***, hypernatremia, ***alkalosis***, low renin, high aldosterone
    - Potassium and hydrogen secretion (in urine) is in exchange for sodium reabsorption
- Screening: ***serum potassium (< 3) and aldosterone to plasma renin activity ratio (> 20:1)***
    - Primary hyperaldosteronism: ***low renin***
    - Secondary hyperaldosteronism: ***high renin***
- Confirmation: ***Urinary aldosterone excretion +/- sodium loading x 3 days***
    - Adrenal venous sampling to lateralize etiology of hyperaldosteronism when not clear on imaging

- Tx: functional adenoma: ***adrenalectomy***
    - Preoperatively start potassium sparing diuretics because of profound hypokalemia
- Tx: Bilateral adrenal hyperplasia: ***spironolactone*** or ***eplerenone*** (aldosterone antagonist) - nonsurgical

Primary Hyperaldosteronism

Screen: serum potassium and aldosterone to plasma renin activity ratio

Confirmation: urinary aldosterone excretion +/- sodium loading

| PHEOCHROMOCYTOMA |

- ***Pheochromocytoma***: catecholamine secreting adrenal gland tumor
- ***Paraganglioma***: catecholamine secreting extra-adrenal tumor
    - Common in ***organ of Zuckerkandl*** (located at the bifurcation of the abdominal aorta or origin of the inferior mesenteric artery)
- Dx: episodic headache, tachycardia, diaphoresis, palpitations, paroxysmal HTN, flushing, nausea, vomiting, chest pain, cardiomyopathy
    - In pregnancy, high risk of maternal and fetal mortality
        - If early in pregnancy: terminate pregnancy and excise the pheochromocytoma
        - If late in pregnancy: caesarian section with excision of pheochromocytoma at the same time; do not allow vaginal delivery as this may cause sudden, massive androgen release
- Factors to induce attacks: tyramine rich foods (beer, cheese, wine), nicotine (cigarettes), anesthesia (e.g. propofol), cocaine
- Histology: Zellballen pattern, ***Chromogranin A***
- Lab: elevated catecholamines / metanephrines, hyperglycemia

- Screening: ***plasma free fractionated metanephrines*** (sensitivity near 99%)
- Confirmation: ***24-hour urine catecholamines*** (specificity near 99%); if inconclusive confirmation test, then proceed with either:
  - o ***Clonidine suppression test*** (0.3mg, recheck metanephrines in 3 hours)
    - * Pheochromocytomas = no suppression
    - * Essential hypertension = approximately 50% reduction of catecholamines
  - o ***Glucagon stimulation test*** (2mg IV; recheck metanephrines in 3 hours)
    - * Pheochromocytomas = increased catecholamines
- Additional Imaging:
  - o ***Iodine-131-labeled metaiodobenzylguanidine (MIBG)***: radionuclide study that highlights elevated levels of norepinephrine
    - * Useful in extra-adrenal tumors, metastatic tumors, or multiple pheochromocytomas
  - o MRI: ***light bulb sign on T2***
- Tx: ***adrenalectomy***
  - o Preoperatively (1st) alpha blockade – phenoxybenzamine x ~ 2 weeks; (2nd) beta blockade after appropriate alpha blockade – propranolol; (3rd) ***aggressive intravenous hydration***!!! Consider preoperative admission for anesthesia evaluation and pretreatment.
  - o If nonmalignant, excised, and asymptomatic = observation
  - o If malignant (excised, unresectable, or symptomatic) = chemotherapy
    - * Cyclophosphamide, vincristine, and dacarbazine
    - * ***Metyrosine***: tyrosine hydroxylase inhibitor (decreases catecholamine synthesis)

Pheochromocytoma Excision

Ligate the adrenal vein first! Likely to have immediate decrease in blood pressure; treat with aggressive hydration

"Dissect the body from the adrenal gland" – do not manipulate the adrenal gland until vascular control

RULE OF 10'S

- 10% pediatric (increased bilateral tumors in kids)
- 10% bilateral
- 10% malignant (defined by metastasis, not local invasion)
- 10% normotensive
- 10% extra-adrenal (increased risk of malignancy)
- 10% familial (increased risk of bilateral and malignancy)

FAMILIAL PHEOCHROMOCYTOMA

- ***von Hippel-Lindau***
    - 3p25 (renal tumors)
- ***von Recklinghausen's disease (Neurofibromatosis 1)***
    - 5% of pheochromocytomas
- ***MEN 2 Syndrome ("PTC syndrome")***
    - RET oncogene on 10q11
    - ***MEN 2A (Sipple Syndrome)***
        - Pheochromocytoma, medullary Thyroid Carcinoma, parathyroid hyperplasia / adenoma
    - ***MEN 2B***
        - Pheochromocytoma, medullary Thyroid Carcinoma, mucosal and gastrointestinal neuroma, marfanoid features
- ***Tuberous Sclerosis***
    - Adenoma sebaceum, seizures, mental retardation, AML

- ***Sturge-Weber Syndrome***: port wine stain, seizures, mental retardation, AVM (arteriovenous malformation)

Pheochromocytoma

Screen: plasma free fractionated metanephrines

Confirmation: 24-hour urine catecholamines

(If inconclusive, clonidine suppression or glucagon stimulation test)

| CUSHING'S SYNDROME |

- ***Cushing's Syndrome***: elevated cortisol
  - MC etiology: exogenous source (i.e. steroid supplementation)
- ***Subclinical Cushing's Syndrome***: excessive cortisol without signs / symptoms
- ***Cushing's Disease***: excessive cortisol secondary to elevated anterior pituitary secreted ACTH
- ***Ectopic Cushing's Syndrome***: excessive cortisol secondary to non-pituitary secreted ACTH (e.g. small cell lung carcinoma, carcinoid)
- ***ACTH-Dependent Cushing's Syndrome*** (80%) – high ACTH level
  - Cushing's Disease
  - Ectopic ACTH or CRH syndrome (Most common: lung, thymus, pancreas)
- ***ACTH-Independent Cushing's Syndrome*** (20%) – low ACTH level
  - Adrenal adenoma
  - Adrenal carcinoma
  - Micronodular / Macronodular hyperplasia (rare; usually bilateral)
- ***Pseudo-Cushing's Syndrome***
  - Major depressive disorder
  - Alcoholism

- Sx: truncal obesity, HTN, diabetes mellitus, proximal weakness, hirsutism, purple striae, moon facies, osteoporosis, easy bruising
- Lab: hyperglycemia, elevated cortisol
- Screening options:
  - ***1mg (low dose) dexamethasone suppression test***
    - Positive if cortisol > 1.8mcg/dL (50 nmol/L)
  - ***24-hour urinary free cortisol*** (test at least twice)
    - Positive if > 3x normal
  - ***Late night salivation cortisol test*** (test at least twice)
    - Positive if elevated (normally diurnal, and should be low)
- Confirmation:
  - ***Late afternoon or midnight ACTH level***
    - < 5 pg/dL ACTH independent (i.e. adrenal adenoma)
    - 5-10 pg/dL indeterminate
    - > 15 pg/dL ACTH dependent (i.e. pituitary vs. ectopic)
- If ACTH Dependent: ***8mg (high dose) dexamethasone suppression test***
  - > 50% suppression: pituitary adenoma (i.e. Cushing's disease)
  - < 50% suppression: ectopic etiology
    - MC is lung etiology
- ***Cortisol Releasing Hormone Test***
  - Cushing syndrome vs. Pseudo-Cushing Syndrome
    - Cushing syndrome: cortisol > 1.4 mcg/dL (38 nmol/L)
    - Pseudo-Cushing Syndrome: cortisol < 1.4 mcg/dL (38 nmol/L)
  - Pituitary adenoma vs. ectopic etiology
    - Pituitary adenoma: ACTH > 50% rise with cortisol > 20% rise
    - Ectopic etiology: no response of ACTH or cortisol
- Additional imaging: Iodocholesterol Scan – identifies ectopic steroid producing tumors
- Surgical Tx: primary resection – adrenalectomy, transsphenoidal

hypophyseal microsurgery, ectopic tumor resection

  - Preoperatively administer stress-dose steroids and tight glycemic control
  - Intraoperative steroids may be needed if hypotension
  - Post-operative steroid taper likely needed until remaining adrenal gland(s) restore function (i.e. avoid adrenal insufficiency)

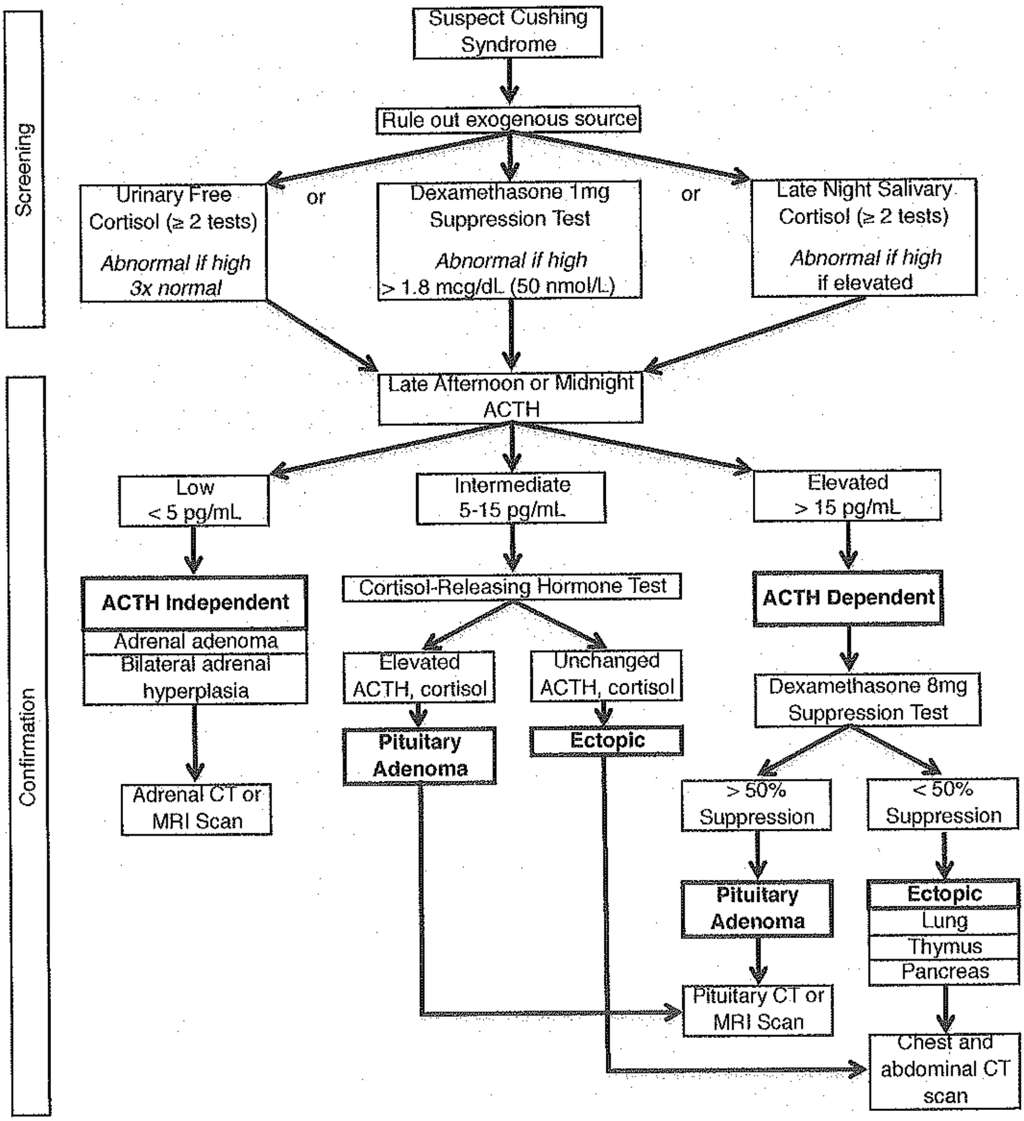
- Medical Tx: only if unresectable; all medications below inhibit precursors of cortisol
    - ***Aminoglutethimide***: inhibits cholesterol conversion to pregnenolone
    - ***Metyrapone***: inhibits 11-beta-hydroxylase
    - ***Ketoconazole***: inhibits cholesterol side-chain cleavage
    - ***Mifepristone***: cortisol and progesterone receptor blockers

Cushing's Syndrome

Screen: 1mg dexamethasone suppression test, 24-hour urinary free cortisol, or late night salivation cortisol test

Confirmation: late afternoon or midnight ACTH level

CUSHINGS SYNDROME WORKUP ALGORITHM


Screening
Confirmation
Suspect Cushing Syndrome
Rule out exogenous source
Urinary Free Cortisol (≥ 2 tests)
Abnormal if high 3x normal
or
Dexamethasone 1mg Suppression Test
Abnormal if high > 1.8 mcg/dL (50 nmol/L)
or
Late Night Salivary Cortisol (≥ 2 tests)
Abnormal if high if elevated
Late Afternoon or Midnight ACTH
Low < 5 pg/mL
Intermediate 5-15 pg/mL
Elevated > 15 pg/mL
ACTH Independent
Adrenal adenoma
Bilateral adrenal hyperplasia
Adrenal CT or MRI Scan
Cortisol-Releasing Hormone Test
Elevated ACTH, cortisol
Unchanged ACTH, cortisol
Pituitary Adenoma
Ectopic
ACTH Dependent
Dexamethasone 8mg Suppression Test
> 50% Suppression
< 50% Suppression
Pituitary Adenoma
Ectopic
Lung
Thymus
Pancreas
Pituitary CT or MRI Scan
Chest and abdominal CT scan

NELSON'S SYNDROME

- Pituitary tumor post-bilateral adrenalectomy (20%)
    - Usually chromophobe adenoma
- Elevated ACTH (lacks negative feedback)
- Hyperpigmentation, headaches, visual changes

| ADRENOCORTICAL CARCINOMA |

ADRENOCORTICAL CARCINOMA

- Rare; usually solitary and unilateral
- Majority are > 6 cm in diameter; calcification is worrisome

Adrenal Neoplasms

Metastasis to the adrenal gland is more common than primary adrenal carcinoma

- **Metastatic lesion etiologies**: Melanoma, breast, lung cancer, renal are common
- ***Lymph node metastasis*** usually to para-aortic, peri-aortic and retroperitoneal regions
- ***Distant metastasis*** usually to liver, lung and retroperitoneum
- For detailed staging information: http://www.cancer.net/cancer-types/adrenal-gland-tumor/staging
- **Weiss Criteria**: nine pathologic criteria that differentiates adrenocortical carcinoma from adenoma
  1. Fuhrman grade 3-4
  2. Mitotic rate > 5/hpf
  3. Atypical mitotic figures
  4. ≤ 25% cytoplasm within cells
  5. > 1/3 diffuse growth pattern
  6. Necrosis
  7. Venous invasion
  8. Sinusoid invasion
  9. Tumor capsule invasion
- Nearly 60% of adrenal carcinomas are functional
  - Most common: Cushing's syndrome

- Tx: En bloc resection ***after ruling out pheochromocytoma***, possible metastasectomy
    - o ***Mitotane (ortho, para –DDD)*** – no survival improvement; however, 1/3 tumor shrinkage and ¾ hormone reduction in functional tumors

Adrenal Surgical Intervention Indications

All adrenal tumors > 5cm

All functional adrenal tumors

Suspect adrenal carcinoma

| ADRENAL INSUFFICIENCY |

ADDISON'S DISEASE (ADRENAL INSUFFICIENCY)

- Absent or low glucocorticoid (cortisol) and/or mineralocorticoid (aldosterone)
- Etiologies: adrenal autoimmune reaction (21-hydroxylase antibodies); tuberculosis; adrenal hemorrhage; malignancy; infection; steroid withdraw; post-adrenalectomy (consider in radical nephrectomy as well because the adrenal may be included in the dissection); sepsis
- Sx: hypotension unresponsive to fluid resuscitation, diffuse abdominal pain
- Lab: hyponatremia, hyperkalemia, azotemia
- Tx: hydrocortisone 100mg every 8 hours; fludrocortisone 0.1 mg daily

| MISCELLANEOUS |

MYELOLIPOMA

- Benign, nonfunctional adrenal tumor composed of bone marrow and adipose elements
    - Do not confuse with angiomyolipoma, which is almost exclusively found in the kidney
- Tx: removal if symptomatic (e.g. pain) or > 7cm

WATERHOUSE-FRIDERICHSEN SYNDROME

- Hemorrhagic adrenalitis
- Neisseria meningitidis

SHEEHAN'S SYNDROME

- Post-partum hypopituitarism secondary to necrosis / hypoperfusion

BILATERAL ADRENAL SPONTANEOUS HEMORRHAGE

- Refractory HTN, adrenal insufficiency / crisis
- Etiology: venous thrombosis (hypercoagulable states), anticoagulation (e.g. warfarin), disseminated intravascular coagulation
- Tx: Hydrocortisone, IV fluids, may continue anticoagulation if stable hemoglobin

FUNCTIONAL ADENOMA LAB TESTING SUMMARY

Primary Hyperaldosteronism (Conn's Syndrome)	
Serum potassium	< 3
Aldosterone : plasma renin activity ratio	> 20: 1
Aldosterone	> 15
Plasma renin activity	< 2
Pheochromocytoma	
Glucose	Elevated
Plasma free fractionated metanephrines	Elevated
24-hour urine catecholamines	Elevated
Clonidine suppression test	No suppression
Hypercortisolism (Cushing's Syndrome)	
1mg dexamethasone suppression test	Cortisol > 1.8 mcg/dL
24-hour urinary free cortisol	> 3x normal
Late afternoon or midnight ACTH	
- Adrenal etiology	Low ACTH (< 5 pg/mL)
- Pituitary or ectopic etiology	High ACTH (> 15 pg/mL)
High dose dexamethasone suppression test	
- Pituitary etiology	> 50% suppression
- Ectopic etiology	< 50% suppression

CHAPTER 6: RENAL TUMORS

| BENIGN |

BENIGN RENAL CYSTS

- Benign, simple cysts = 70% all asymptomatic renal masses
- 50% of patients older than 50 have renal cysts
- Growth rate is estimated at 2.8 mm / year
- If large or painful: drainage ± sclerosis; laparoscopic unroofing
    - 95% ETOH = 90+% successful ablation
- ***Peripelvic or renal sinus cysts***: originates from ***lymphatics*** rather than parenchyma
- **Bosniak Classification** is based on CT imaging
    - ***Hyperdense cyst*** with have elevated Hounsfield units (HU) on non-contrast CT with similar HU on contrast CT (i.e. no enhancement)
    - See the Urologic Radiology chapter for the table on Bosniak Classification and management.

POLYCYSTIC KIDNEY DISEASE

- ***Autosomal dominant*** (90%), diagnosed as adult with renal and hepatic cysts
    - Chromosome 16p (PKD1; polycystin-1) and chromosome 4 (PKD2; polycystin-2)
- ***Cortical renal cysts*** which are not contiguous with collecting tubules;

therefore, the urinary analysis may be negative when the cysts are infected

  - Lipophilic antibiotics penetrate the cysts better: ***ciprofloxacin, trimethoprim/sulfamethoxazole, clindamycin, chloramphenicol***
  - If unable to clear infection, consider percutaneous drainage
- May have flank pain, hematuria, nephrolithiasis, UTI
- 40-50% will have renal failure needing dialysis or transplant
- Associated with ***Berry aneurysms***
  - Screen with MRA after age 30
- No increase in renal cell carcinoma
- ***Autosomal recessive*** (10%), rare, diagnosed as a child, causes early renal failure
  - Chromosome 6 (PKHD1, fibrocystin)
  - Associated with congenital hepatic fibrosis and biliary atresia
  - Lacks cysts in other organs (auto-dominant has cysts in other visceral organs)

NEPHRONOPHTHISIS

- ***Medullary*** cystic disease formed at the corticomedullary junction
- Rare, autosomal recessive mutation in ciliary proteins
- Forms: infantile, juvenile (MC), and adolescent
- ESRD progression inevitable
- Juvenile is associated with ***retinitis pigmentosa***
- Tx: supportive care

MEDULLARY SPONGE KIDNEY (MSK)

- Benign congenital disorder with multiple cysts in ***collecting ducts***
- ***RET oncogene;*** majority sporadic
- Sx: hematuria, nephrolithiasis, UTI, ***nephrocalcinosis***
  - Other causes of nephrocalcinosis: hyperparathyroidism, Distal RTA (type 1), renal TB, papillary necrosis, hyperoxaluria
- Usually asymptomatic until age 30-40 (many remain asymptomatic)

- ***"Paint brush-like"*** appearance of calyces on KUB
- Associated with Beckwith-Wiedemann Syndrome / hemihypertrophy
- Up to 20% of stone formers may have some element of MSK
- Tx: No treatment for cysts. Focus on infections and calculi removal / prevention
    - May benefit from thiazide diuretic if hypercalciuria

Nephrocalcinosis Etiologies

Hyperparathyroidism, distal RTA (type 1), renal TB, papillary necrosis, hyperoxaluria, medullary sponge kidney

MULTICYSTIC DYSPLASTIC KIDNEY (MCDK)

- Sporadic, benign, congenital renal maldevelopment characterized by multiple cortical cysts that renders the kidney ***non-functional*** with an absent calyceal system
- Usually unilateral with contralateral renal hypertrophy as infant and normal renal function; bilateral is not compatible with life
- DDx: Severe ureteropelvic junction obstruction (UPJO)
    - Nephronophthisis = autosomal recessive, late onset renal failure (30 years old)
- May have slight increased risk of Wilm's tumor (NNT near 2,000)
- High incidence (up to 33%) of contralateral vesicoureteral reflux ***(recommend screening with VCUG);*** may also have associated contralateral UPJO
- Tx: No treatment usually; the kidney will likely involute
    - Nephrectomy if uncontrolled hypertension, pain or shortness of breath for diaphragm irritation

ONCOCYTOMA

- 3-7% solid renal masses; derived from ***distal tubules***
    - Chromophobe RCC is also originates from distal renal tubules; therefore, they have similar histologic findings

- Benign, but RCC ipsilateral or contralateral kidney in up to 30%
- Central scar is common; radiographically cannot distinguish from RCC
- Loss of chromo 1 and Y, loss of heterozygosity on 14q, rearrangements at 11q13
- ***Birt-Hogg-Dube Syndrome:*** oncocytoma, chromophobic RCC, cutaneous fibrofolliculoma, pulmonary cysts
- Tx: partial/radical nephrectomy or thermal ablation

ANGIOMYOLIPOMA (AML)

- Benign tumor derived from perivascular epithelioid cells with ***adipose*** tissue, ***smooth muscle*** and ***blood vessels***
- Epithelioid variant has paucity of fat with 1/3 having malignant potential
- Strong female predilection (near 80%)
- If ***negative HU on CT*** (fat) is pathognomonic for AML (never calcification)
- MRI: chemical shift imaging (in/out of phase) there is a decrease in enhancement
- Histologic stain ***HMB-45 positive*** (melanoma positive also)
- **Wunderlich syndrome** = massive retroperitoneal hemorrhage; occurs in 10% of AMLs and more likely in pregnancy
  - Lenk's Triad: acute flank pain, evidence of internal bleeding (e.g. tachycardia, hypovolemic shock), palpable tender abdominal mass
  - ***Grey Turner's sign***: flank ecchymosis
  - ***Cullen's sign***: umbilical ecchymosis
  - Most common etiology of retroperitoneal hemorrhage: abdominal aortic aneurysm, renal cell carcinoma, angiomyolipoma
- Tx: ***if > 4 cm then partial/radical nephrectomy or embolization*** (consider early intervention in young female desiring pregnancy)
  - If epithelioid variant, surveillance imaging similar to partial nephrectomy for RCC; currently no medical treatment available (case reports of Everolimus as treatment)

TUBEROUS SCLEROSIS (TS)

- 20-25% of patients with AMLs have TS
- ***Sebaceous adenoma, seizures, mental retardation, AMLs (80%)***
  - "Zits, fits, deficits"
- Autosomal dominant; ***9q34 (TSC1); 16p13 (TSC2)***
- AML normal 5% annual growth rate; TS has 20% annual growth rate
- TS has slight increased risk of renal cell carcinoma
- ***Everolimus*** (mTOR inhibitor) indicated for AMLs in TS (also treats subependymal giant cell astrocytoma (SEGA) seen in TS, and poor risk RCC)

MIXED EPITHELIAL STROMAL TUMOR OF THE KIDNEY (MESTK)

- Bosniak 3-4 cystic renal mass
- Perimenopausal women, related to estrogen therapy
- ***Stain positive for ESTrogen / progesterone receptors***
- Tx: partial / radical nephrectomy

PAPILLARY ADENOMA

- Benign renal cortical lesion
- Must be < 5mm (***if > 5mm = papillary renal cell carcinoma***)
- Trisomy chromo 7 and 17 (papillary RCC)
- At 3cm, only 5% have metastases
- Tx: partial/radical nephrectomy or thermal ablation

METANEPHRIC ADENOMA

- Usually incidental finding around age 40, however may occasionally have "RCC triad = hematuria, flank pain, abdominal mass"
- Benign with rare, aggressive variants
- Tx: partial/radical nephrectomy or thermal ablation

RENINOMA

- Rare, renin-secreting ***juxtaglomerular tumor***
- Elevated renin, i.e. up-regulated RAAS system, therefore HTN, hypokalemia (aldosterone), polydipsia, polyuria, nocturia, headaches (HTN)
- Young females with secondary HTN (***rule out renal artery disease***)

LEIOMYOMA

- Rare, benign, smooth muscle tumor
- Origin: renal capsule or peripelvic tissues, less often renal vein
- Tx: radical or partial nephrectomy, nephroureterectomy (pelvic tumor)

| MALIGNANT |

RENAL CELL CARCINOMA

- Incidence 1:70; mortality 35-40% (most deadly genitourinary tumor)
    - o Majority are incidental findings
    - o Classic triad (palpable mass, hematuria, flank pain) is relatively uncommon (<15%)
- Increased incidence in HTN, ESRD, Tuberous Sclerosis, obesity (1/3)
- Majority are ***adenocarcinoma***
- Most common subtypes: (1) clear cell carcinoma (2) papillary (3) chromophobe
- Transition cell carcinoma accounts for 10% of renal tumors
- 25-33% of patients with RCC will have metastatic disease at presentation
- Histologic good prognostic findings: increased CA-IX, low vimentin, low p53
    - o Any variant with sarcomatoid features has poor prognosis
- 95% are sporadic, 5% are familial
    - o ***All familial RCC disorders are autosomal dominant***

- RCC in kids = rare; usually papillary
- RCC in ESRD = increased incidence; usually papillary (associated with acquired cystic renal disease)
    - o Renal ultrasound recommended annually after 5 years of dialysis
- Physical findings
    - o Neurologic findings: obtain brain CT scan
    - o Dermatologic findings: consider hereditary RCC
    - o Rapid onset of varicocele, particularly right-sided are suspicious for RCC
- ***Renal biopsy: consider in small renal masses < 4 cm.***
    - o Why small renal masses? 20% benign, 60% indolent malignancy, 20% aggressive malignancy
    - o Low false negative (1%) and complications rates (< 2%); needle-tract seeding is extremely rare
    - o Classically, biopsy if concerned for ***metastasis, abscess, or lymphoma***
        - * If lymphoma, proceed with chemotherapy (no further surgery)

RCC Biopsy Indications

Small renal masses (< 4 cm)

Metastasis

Abscess

Lymphoma

- Workup
    - o ***CT scan*** with enhancement ***≥ 20 HU*** and no fat (i.e. angiomyolipoma)
        - * ***MRI scan*** if renal vein or IVC involvement
    - o ***Chest x-ray*** in all patients; ***CT scan chest*** if inconclusive x-ray

  - ***CT brain*** if neurologic findings / complaints
  - ***Bone scan*** if elevated alkaline phosphatase, bone pain, pathologic fracture
  - ***Mammogram*** for women to rule out breast cancer primary

MULTILOCULAR CYSTIC RENAL CELL CARCINOMA

- Purely cystic tumor lined by RCC clear cells (no solid component, just cyst lining)
- Associated with ***VHL***
- DDx: benign cystic disease, MESTK, cystic Wilm's tumor in children
- No recurrence or metastasis reported after resection
- Tx: partial / radical nephrectomy

CLEAR CELL - RCC

- Tumor suppressor gene of ***VHL gene*** at ***3p25-26***
- Arises from ***proximal tubules*** of the nephron
- VHL gene suppresses the ***hypoxia inducible factor (HIF-1)*** normally
  - Under hypoxic situations, HIF-1 stimulates to angiogenesis, glucose transport and autocrine growth stimulation (VEGF, Glut1, PDGF). This ultimately leads to neovascularization and tumor growth.
  - Pathways for tyrosine kinase inhibitors, mTOR inhibitors, VEGF inhibitor
- P53 and PTEN/Akt pathway also associated with clear cell RCC

PAPILLARY TYPE 1 - RCC

- Proto-oncogene of ***cMet*** gene at ***7q31*** (NOTE: only familial RCC proto-oncogene)
  - cMet (aka scatter factor) regulates proliferation and differentiation of renal epithelial and endothelial cells
- Arises from ***proximal tubules*** of the nephron
- Histology: ***basophilic*** (blue); low grade
- Tx: partial / radical nephrectomy or thermal ablation

PAPILLARY TYPE 2 - RCC

- Tumor suppressor gene of ***fumarate hydratase*** at ***1q42-44*** (Krebs cycle enzyme)
- Arises from ***proximal tubules*** of the nephron
- Histology: ***eosinophilic*** (pink), more aggressive appearing
- Tx: partial / radical nephrectomy or thermal ablation

CHROMOPHOBE - RCC

- Tumor suppressor gene of ***folliculin*** at ***17p11.2***
- Arises from ***distal tubules*** of the nephron (closely resembles oncocytoma; some suggest the two tumors are on a spectrum of distal tubule tumors)
- Histology: perinuclear halo (Koilocyte-like) with raisinoid nuclei; **Hale's Colloidal +** (blue stain); **diffuse CK7 staining** (oncocytoma CK7 is sparse)
    - o Few mitochondria and many microvesicles (note: Oncocytoma has many mitochondria and few microvesicles)
- Tx: partial / radical nephrectomy or thermal ablation

RENAL MEDULLARY CARCINOMAS

- Sickle cell patient (African Americans) - medulla is most sensitive to hypoxia because last area to receive blood flow in the kidney
- Young adults with locally advanced / metastatic disease at presentation
- Highly aggressive with mean survival of 12-15 months
- Tx: radical nephrectomy

METASTASIS

- Most common metastatic lesion to the kidney: lung carcinomas
    - o Contralateral kidney, breast, gastrointestinal tract are other sources
- Most common RCC metastatic sites: (1) lung (2) bone (3) liver

REPRESENTATION OF RENAL CELL CARCINOMA TYPES

Tumor Type	Percent of RCC
Clear cell	75%
Papillary	10-15%
Chromophobe	5%
Oncocytoma	5%
Miscellaneous	1-2%

| FAMILIAL RCC |

VON HIPPEL-LINDAU DISEASE (VHL)

- Tumor suppressor gene of ***VHL gene*** at ***3p25-26***
- VHL complex: ***RCC - clear cell*** type (50%), ***pheochromocytoma***, retinal angiomas, nervous system hemangioblastomas
    - Epididymal cystadenomas are common and benign
- Type 1 VHL: low risk for pheochromocytoma
- Type 2 VHL: high risk for pheochromocytoma
- Bilateral, multifocal, recurrent RCC is common
- All cysts in VHL have malignant potential
- Tx: partial nephrectomy when tumors > 3cm

HEREDITARY PAPILLARY RCC (HPRCC)

- ***Papillary type 1 RCC***
- Trisomy 7 and 17
    - Urinary FISH may be positive because it probes for chromosomes 3, **7**, 9p21, **17**

- Less aggressive than papillary type 2
- Tx: partial / radical nephrectomy or thermal ablation

HEREDITARY LEIOMYOMATOSIS AND RCC (HLRCC)

- ***Cutaneous and uterine leiomyomata, and papillary type 2 RCC*** (10-20%)
- Usually solitary and unilateral RCC
- Tx: partial / radical nephrectomy or thermal ablation (treat aggressively as this tumor metastasizes quickly)

BIRT-HOGG-DUBE SYNDROME

- Mutation of ***folliculin*** gene on chromosome ***17p11***
- ***Chromophobic RCC and/or renal oncocytomas, cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax***
- Renal tumors 20-30% of patients
- Tx: partial / radical nephrectomy or thermal ablation

HEREDITARY RENAL TUMOR FINDINGS

Tumor	Chromosome	Stain	Etiology
Clear cell	VHL 3p24-35	CD10 (95%) Vimentin (80%)	Proximal tubule
Papillary type 1	c-Met 7q31 (7, 17) (only proto-oncogene)	AMACR (100%) Basophilic - blue	Proximal tubule
Papillary type 2	Fumarate hydratase 1q42	AMACR (100%) Eosinophilic - pink	Proximal tubule
Chromophobic	BHD 17p11.2 (LOH) MC LOH 3p25-26	Hales colloidal; diffuse CK7 (oncocytoma sparse)	Distal tubule
Bellini duct	Multiple	Ulex europaeus (99%) 34bE12 (99%) Vimentin (100%)	Collecting duct
AML	TS1 9q34 TS2 16q13	HMB-45	Endothelium, smooth muscle, fat
RCC Xp11.2 translocation / TFE3 gene fusions	Xp11.2	Psammoma bodies	Adolescents

PARANEOPLASTIC SYNDROMES

- Seen in approximately 1/3 of patients with RCC

  - It does not necessarily indicated metastatic disease; however, may indicate advanced disease
- ***Hypercalcemia***: elevated calcium levels secondary to ***parathyroid hormone-related peptide*** (PTHrP) and PTH in the absence of bone metastasis; most common RCC paraneoplastic syndrome
  - Tx: loop diuretic; bisphosphonates; nephrectomy
  - Differentiate between RCC with metastatic bone disease resulting in hypercalcemia (50%), which is not a paraneoplastic syndrome
- ***Stauffer Syndrome:*** hepatic dysfunction in patients with non-metastatic RCC
  - Majority will resolve after primary tumor resection
- ***Polycythemia***: elevated erythropoietin
- ***Anemia***: poor nutritional status from chronic disease, and elevated lactoferrin (binds iron)
  - Anemia is more common in patients with RCC than polycythemia
- ***Hypertension***: elevated renin levels leads to activation of the renin-angiotensin-aldosterone system; most commonly seen in low grade, clear cell RCC
  - Tx: nephrectomy
- ***Constitutional symptoms***: fever, chills, night sweats, weight loss, fatigue

| RCC STAGING |

- Be sure to know the difference in staging in relation to tumor size
  - ≤ 4cm (T1a)
  - 4 – 7cm (T1b)
  - > 7 – 10cm (T2a)
  - > 10cm (T2b)
- Be able to differentiate T3 (venous tumor thrombus)
  - T3a: renal vein / sinus

- T3b: vena cava below the diaphragm
- T3c: vena cava above the diaphragm

- Adrenal involvement
    - ***Direct extension = T4***
    - ***Indirect involvement (i.e. metastasis) = M1***
- For detailed staging information: http://www.cancer.net/cancer-types/kidney-cancer/staging-illustrations

FUHRMAN NUCLEAR GRADING

- High prognostic value
- If any sarcomatoid findings, automatically upgraded to Grade 4

RISK BASED ON HISTOLOGY

- **Favorable**: Chromophobe, Papillary type 1 grade 1
- **Intermediate**: Clear cell grade 1-2, Papillary type 1 grade 2
- **Unfavorable**: Clear cell grade 3-4, Papillary type 2, Any tumor with sarcomatoid features

| RCC TREATMENTS |

RENAL CELL CARCINOMA SURGICAL INTERVENTIONS

- RCC is considered primarily a surgical disease, as chemotherapy and radiation have not been successful treatments.
- In select small renal masses, active surveillance is an option; however, not all malignancies grow prior to metastatic behavior
- ***R.E.N.A.L. Nephrometry Score***: nomogram to assess the complexity of a renal tumor, and is predictive of surgical outcomes / morbidities
    - **Radius**: ≤ 4cm vs. 4-7cm vs. ≥ 7cm
    - **Exophytic**: ≥ 50% vs. < 50% vs. completely endophytic
    - **Nearness to collecting system/renal sinus**: ≥ 7mm vs. 4-7mm vs. ≤ 4mm

  - o **Anterior/Posterior**: anterior vs. posterior vs. neither vs. hilar
  - o **Location**: above/below polar lines vs. crosses polar line vs. > 50% of mass crosses polar line or mass crosses axial renal midline or mass completely between polar lines
  - o Scoring:
    - * 4-6: low
    - * 7-9 moderate
    - * 10-12: high

- Thermal ablation is usually only reserved for masses < 4cm (T1a)
- **Stages 1-3**: the recommendation is partial / radical nephrectomy or thermal ablation pending size, location, co-morbidities, surgeon preference.
  - o Partial nephrectomy indications: bilateral tumors, tumor in solitary kidney, small renal masses (< 4cm), decreased renal function or co-morbidities that lead to renal function (e.g. hypertension, diabetes)
  - o Partial nephrectomy keys: early and complete vascular control, diuresis (Mannitol), ***ischemia time*** – goal is < 30 minutes of warm ischemia, adequate renal reconstruction to avoid urine leak and/or post-operative bleeding
    - * ***Mannitol***: used with partial nephrectomies prior to hilar clamping to reduce oxidative damage and free radicals, and induce diuresis
- **Stage 4**: if surgically resectable, solitary metastasis = nephrectomy + metastasectomy; however if multiple metastases = cytoreductive nephrectomy and medical therapy.
  - o < 1% of cytoreductive nephrectomy result in spontaneous metastatic regression
  - o If not medically cleared, surgically unresectable, or brain metastasis = medical therapy only
- Regional lymph node dissection is optional, but recommended if gross adenopathy
- Adrenal gland removal should NOT be removed unless the renal tumor has direct extension (T4). Controversy if removal is indicated for upper pole tumors without direct extension or tumors > 7 cm (T2)

POST-SURGICAL FOLLOW UP

- Timing is variable (age of patient, pathologic stage, aggressiveness of tumor, etc.)
- Recurrence usually within the 1st 2 years after surgery
- Most common sites of recurrence: (1) lung (2) bone (3) liver

AUA RCC FOLLOW-UP GUIDELINES

Patient	Baseline Postoperative CT Scan	Follow-up Abdominal CT Scan	Chest X-ray or CT Scan
pT1, N0, Nx	3-12 months	Annually x 3 years (partial Nx) Physician discretion (radical Nx)	Annually x 3 years
pT2-4, Nany	3-6 months	Semiannually x 3 years, annually x 2 years	Semiannually x 3 years, annually x 2 years
Ablation*	3-6 months	Annually x 5 years	Annually x 5 years
Active Surveillance*	6 months from diagnosis or biopsy	Annually	Annually (if biopsy proven RCC)

** Consider renal tumor biopsy with active surveillance patients; all tumors undergoing ablation should have a pretreatment tumor biopsy*

- ***Hyperfiltration injury***: reduction of one renal unit leads to increased perfusion, thus hyperfiltration of the remaining renal unit(s); may be months to years
    - Removal of ***> 75%*** of function renal tissue is concerning for hyperfiltration injury
    - May lead to focal segmental sclerosis that progresses to renal failure in time
    - ***Proteinuria*** is first indicator (related to amount of resection)

    - Leads to ***hypertension***
- ***Urine leak***: after partial nephrectomy
    - Maintain or establish drainage (e.g. Jackson-Pratt drain, Double-J ureteral stent)
- Radical nephrectomy compared to partial nephrectomy results in higher ***cardiovascular disease*** and ***chronic renal insufficiency/failure***
    - Driving force behind partial nephrectomy for small renal masses
- ***Post-operative bleeding***: monitor hemoglobin/hematocrit and vital signs closely

RENAL CELL CARCINOMA MEDICAL TREATMENT

- Palliative radiotherapy, bisphosphonates, RANK ligand inhibitors for bony metastases, pain control, clinical trials, and hospice may be considered in all patients
- Medications listed have been studied for clear cell - RCC; however, many use them in other RCC types.

RCC Treatment Pathway

Hypoxia-inducing Factor 1(HIF-1) stimulates pathways to allow for angiogenesis, tumor growth, and glucose transport. Tyrosine kinase inhibitors, mTOR inhibitors, and VEGF ligand inhibitors all impact this pathway to impact tumor growth.

TYROSINE KINASE INHIBITORS

SUNITINIB

- 11 months vs. 5 months PFS compared to Interferon-alpha
- 50mg oral daily, 4 weeks on / 2 weeks off (may dose reduce according to side effects)

SORAFENIB

- 5.5 months vs. 2.8 months PFS compared to placebo (TARGET study)
- 400mg oral BID (may reduce to daily or every other day as needed)

PAZOPANIB

- COMPARZ study underway regarding PFS of Sunitinib vs. Pazopanib
- 800mg oral daily

CLASS SIDE EFFECTS

- ***Hand-foot syndrome*** (desquamation), diarrhea, fatigue, ***hepatotoxicity***, left ventricular dysfunction/heart failure

MTOR INHIBITOR

TEMSIROLIMUS

- 25mg IV weekly
- Indicated for ***poor risk patients*** with advanced RCC
    - LDH > 1.5X normal level (bulky disease)
    - Anemia
    - Hypercalcemia
    - Interval < 1 year from original diagnosis to the start of systemic therapy
    - Karnofsky performance score ≤ 70
    - ≥ 2 sites of organ metastasis
- 10.9 months vs. 7.3 months median survival compared to Interferon-alpha
- 5.5 months vs. 3.1 months PFS compared to Interferon-alpha
- SE: rash, fatigue, mucositis

CYTOKINE THERAPY

INTERLEUKIN-2 (IL-2)

- Only systemic therapy with 5% durable complete remissions
- Approximate 15% response rate in selected individuals
- Patients need to have excellent performance status; some recommend if only pulmonary metastasis.

INTERFERON-ALPHA (IFN)

- Used in conjunction with Bevacizumab

VEGF LIGAND INHIBITION

BEVACIZUMAB + INTERFERON-ALPHA

- 10.2 vs. 5.4 months PFS compared to placebo + Interferon-alpha
- SE: hemorrhage, fatigue, proteinuria, HTN, ***wound healing complications***
- 10 mg/kg IV infusion every 2 weeks until disease progression
- t1/2 ≈ 20 days; must be stopped at least 28 days prior / after surgery, consider 80-100 days (3 months) to allow for 4-5 half-lives
    - Also discontinue in patient with Fournier's gangrene

SECOND LINE RCC MEDICAL THERAPY

- Everolimus, Axitinib, Sorafenib, Pazopanib, Temsirolimus, Bevacizumab, IFN, IL-2

CHAPTER 7: RENAL PELVIS AND URETERAL TUMORS

UPPER TRACT TRANSITIONAL CELL CARCINONOMA (TCC)

- Represents approximately 5% of all urothelial carcinomas and 10% of all renal tumors
- TCC accounts for > 95% of upper tract carcinoma; remaining types are squamous cell carcinoma (associated with staghorn calculi) and adenocarcinoma
- Most common locations: ***renal pelvis*** > ureter
    - Ureter location: ***distal*** (70%), mid (25%), proximal (5%)
- Present at higher grade / stage than bladder cancer because thinner muscle layer
- Risk factors: same as bladder TCC
    - ***Inverted papilloma*** – found in the bladder, has increase risk of upper tract TCC
    - Upper tract TCC associated with bladder TCC is < 5%; however, may be near 20% in patients with CIS
    - ***Balkan endemic nephropathy***
        - Etiology: ingesting contaminated food with ***aristolochic acid***
        - Renal failure; increased risk of upper tract TCC
- ***Lynch syndrome*** (hereditary non-polyposis colorectal cancer): increased risk of upper tract TCC
    - MSH2, MLH1 genetic mutations
- Sx: hematuria, flank pain (ureteral obstruction)

- Lab: urine cytology +/- ureteral barbotage (high grade TCC and CIS); FISH
    - Suspect if positive cytology with a negative cystoscopy
- Imaging: ***CT urogram***; if renal failure then retrograde pyelogram
    - Suspect if central renal tumor
- Dx: ureteropyeloscopy and biopsy; ureteral barbotage with cytology
- Staging: subepithelial connective tissue (T1), muscularis (T2), surrounding fat or kidney (T3), surrounding organs (T4)
- Lymph nodes:
    - Renal pelvis: renal hilar, paracaval, aortic, retroperitoneal
    - Ureter: renal hilar, iliac, paracaval, periureteral, pelvic
- Metastasis: usually to lung, lymph nodes, bone, and liver
- Tx: ***Grade*** is key to guide treatment options
    - ***Nephroureterectomy with bladder cuff*** has been the gold standard, and remains the treatment of choice for high grade, invasive, or multifocal tumors.
    - Consider ***endoscopic resection/ablation*** in solitary kidney, poor surgical candidate, or especially if ***low grade/stage tumors***
        - * Holmium or Nd:YAG lasers may be used for tumor ablation
        - * Percutaneous approach may be considered in large (> 1.5cm) renal pelvis TCC that are grade 1 and possibly grade 2 (grade 3 tumors require nephroureterectomy)
            - Advantage: after 2 weeks and normal nephrostogram, BCG or Mitomycin may be administered into the collecting system vs. retrograde via reflux up a ureteral stent
            - Disadvantage: ~ 1/3 will recur
    - Distal ureteral TCC – ***distal ureterectomy with ureteroneocystostomy***
    - Muscle invasive: MVAC or gemcitabine and cisplatin chemotherapy
    - Note: BCG / Mitomycin treatment for upper tract TCC is extrapolated from bladder cancer and retrospective studies. There are currently no prospective studies showing improved survival.

- Surveillance: many options, consider every 3-4 months for 2 years, then 6 months for 2 years, then annually
- Urine cytology
- Ureteropyeloscopy

Upper Tract Urothelial Carcinoma Treatment

Gold standard has been a nephroureterectomy with a bladder cuff; however, low-grade tumors may be candidates for endoscopic resection/ablation or ureterectomy

URETERAL ENDOMETRIOSIS

- Rare; genitourinary system involved with 1-5% of endometriosis patients
- Sx: hydronephrosis (usually extrinsic compression)
- Histology: progesterone and estrogen receptor positive
- MRI scan has ~90% sensitivity
- Tx: ***surgical resection*** with concomitant ***hysterectomy with bilateral salpingo-oophorectomy*** is usually need
  - o If only mild symptoms, may consider gonadotropin-releasing hormone agonist (e.g. leuprolide) or medroxyprogesterone

Ureteral Endometriosis

Cyclical pain associated with menstruation and hydronephrosis (40% silent)

FIBROEPITHELIAL POLPS

- Benign ureteral tumors, usually found in the proximal ureter
- Vast majority are found in men and on the left side
- Sx: hematuria, ureteral obstruction (hydronephrosis, renal colic)
- Tx: ureteroscopic removal particularly if at the UPJO; if unable, consider excision with ureteroureterostomy

CHAPTER 8: BLADDER TUMORS

| RISKS |

CIGARETTE SMOKING

- 1/3 of all TCC (transitional cell carcinoma)
- Increased relative risk by 2-4X
- Patients that quite smoking once diagnosed with TCC, do better than those that continue to smoke

EXPOSURES

Aromatic amines (e.g. aniline dyes), ***acrolein***, combustion products, Phenacetin (off market since 1980's)

- Cyclophosphamide metabolite is acrolein, which may cause hemorrhagic cystitis; prevented with ***mesna***
- **Work exposures**: physicians, autoworkers, machinists, dry cleaners, dental tech, plumbers, paper factory
- Pelvic radiation – prostate, cervix, uterus

CHRONIC CYSTITIS

- Chronic indwelling catheters or bladder calculi may lead to ***squamous cell carcinoma (SqCC)***
- ***Schistosoma haematobium*** may lead to SqCC (Bilharzial bladder cancer)
    - Endemic in Egypt, infected by swimming in contaminated water
    - Tx: Praziquantel

NOTE: TCC may have a latency period from exposure of up to 50 years in 20% of patients

| HISTOLOGY |

BLADDER LAYERS

Normal urothelium is 5-7 layers (contracted bladder) and 2-3 cells (distended bladder)

1. Mucosa
    - o **Urothelium**: glycosaminoglycan (GAG) layer, uroplakins, umbrella cells, intermediate stratum, basal cell
        - * ***Ta disease***
    - o **Lamina propria**: connective tissue, muscularis mucosa
        - * ***von Brunn's nests***: benign proliferation of urothelium in the lamina propria layer;
        - * T1 disease
2. Muscularis propria
    - o Inner longitudinal, middle circular, outer longitudinal layers of detrusor
    - o T2 disease
3. Adventitia: majority of bladder except at the dome where there is a serosa layer composed of peritoneum
    - o T3 / T4 disease

| MALIGNANT MOLECULAR MARKERS |

TUMOR SUPPRESSOR GENES

- **P53 on 17p13.1**
    - o ***High grade TCC***
    - o Normally influences damaged DNA cells towards apoptosis

- **P16 (CDKN2) on 9p21**
    - Associated with > 50% of bladder cancers
    - Normally inhibitor of Cdk4-cyclin D complexes (i.e. indirect RB protein activation)
- **P27 (Kip) on 12p13**
    - Aggressive TCC
    - Normally inhibitor of Cdk4-cyclin D complexes (similar to p16)
- **Retinoblastoma (RB) gene on 13q14**
    - Aggressive TCC
    - Normally RB (hypophosphorylated) inhibits cell cycle progression through the G1/S restriction point
- **9q loss**
    - Low grade superficial TCC

PROTO-ONCOGENE

- ***FGFR3*** (Fibroblast Growth Factor Receptor 3)
    - Found in majority (~2/3) of ***low grade TCC***
    - Good prognostic marker (i.e. low potential to progress)
- **RAS gene family**
    - Normally involved with cell cycle regulation
- **ERBB2** or **HER2/neu on 17q12**

NUCLEAR PROLIFERATIVE ANTIGEN

- **Ki-67 on chromosome 10**
    - Aggressive TCC
    - Associated with cell cycle and required for cell proliferation

FISH (FLUORESCENCE IN SITU HYBRIDIZATION)

- Centromeric probes for aneuploidy of chromosomes ***3, 7, 17*** and loss of chromosome ***9p21***
- Approximate sensitivity 50-80%% / specificity 90%
- May have positive months prior to ability to visualize; also papillary RCC may give positive result (chromosome 7, 17)

BENIGN BLADDER LESIONS

INVERTED PAPILLOMA

- Benign; however may indicate TCC elsewhere, particularly the upper tracts

NEPHROGENIC ADENOMA

- Benign, rare; likely primitive renal tubular cells (not to be confused with a renal lesion)
- Metaplastic response to irritation, trauma, radiation
- Tx: transurethral resection / fulguration; however, high recurrence rate

CYSTITIS GLANDULARIS

- Benign secondary to chronic inflammation; there are a few case reports that show an association with adenocarcinoma
- Recommend monitoring and resection of glandularis tissue

CYSTITIS CYSTICA

- Benign; extension of Brunn's nests with cystic spaces within the lamina propria
- Related to irritation of urothelium and treat any infection

MALACOPLAKIA

- Secondary to chronic UTI (vast majority are coliform)
    - May be associated with defective microtubular assembly
    - Decreased cGMP levels may impair phagocytosis
- ***Michaelis-Gutmann bodies*** = basophilic inclusions with calcium and iron
- **von Hansemann cells** = histiocytes (macrophages with Michaelis-Gutmann bodies)
- Dx: biopsy
- May occur in any genitourinary organ; however, most commonly presents in the bladder

  - Renal parenchyma: fever, pain, and/or renal mass
  - Ureter: strictures / obstruction
  - Prostate: rare
  - Testis: unable to differentiate from testicular cancer via ultrasound
- Tx: long-term antibiotics; vitamin C and bethanechol (cholinergic) increase the cGMP to cAMP ratio

SQUAMOUS METAPLASIA (PSEUDOMEMBRANOUS TRIGONITIS)

- Benign changes of urothelium to squamous type secondary to chronic inflammation or infection
- Commonly seen in young women secondary to estrogen exposure, and women with recurrent UTIs

| MALIGNANT BLADDER TUMORS |

LEUKOPLAKIA

- Currently considered a premalignant bladder lesion as it has been associated with a few reports of SqCC
- Histology: keratinizing squamous metaplasia
  - Do not confuse with squamous metaplasia (non-keratinizing) of the trigone commonly seen in women, which is benign
- NOTE: leukoplakia of the vulva and penis if premalignant

CARCINOMA IN SITU (CIS)

- Occurs in approximately 10% of bladder cancer patients; however, only found as an isolated lesion < 5% of all cases of CIS.
- ***Severe dysplasia*** that ranges from a velvety, red mucosa lesion to invisible
  - Mild to moderate dysplasia is usually reactive, and not associated with neoplasia
- May be symptomatic with urgency, frequency, dysuria

- Associated with high-grade tumors that have a high risk to progress to muscle invasive bladder cancer.
- Lab: cytology and FISH (fluorescence situ hybridization)
- Tx: intravesical BCG, early cystectomy for BCG non-responders, Valrubicin

TRANSITIONAL CELL (UROTHELIAL) CARCINOMA (TCC)

- > 90% of all bladder cancer in USA
- Majority are papillary type with the remaining appear nodular or mixed
- Well differentiated tumors are usually superficial, while poorly differentiated tumors are usually muscle invasive
- Staging: mucosa (Ta), lamina propria (T1), muscularis ***propria*** (T2), perivesical fat (T3), surrounding organs (T4)
    - Muscularis ***mucosa*** = T1
    - Prostatic ***stroma*** = T4
        - All other prostatic involvement by bladder TCC is staged according to the depth of bladder involvement (i.e. when staging bladder cancer, ignore prostate involvement, unless stromal)
        - Note: if primary urethral TCC, prostate stromal involvement = T2
- For detailed staging information: http://www.cancer.net/cancer-types/bladder-cancer/staging-and-grading
- ***NMIBC = Non-Muscle Invasive Bladder Cancer***
    - Invades the lamina propria, but not into the muscularis propria (Ta, T1, CIS)
    - 70-80% of NMIBC patients present with NMIBC
    - ***Micropapillary variant***: ominous prognosis, offer immediate cystectomy when NMIBC as it is highly resistance to intravesical BCG and neoadjuvant chemotherapy
    - ***T1 with lymphovascular invasion*** is poor prognostic sign; offer early cystectomy +/- neoadjuvant chemotherapy
    - ***Squamous differentiation***: most common variant; treat as regular TCC

  - ***Sarcomatoid variant***: immediate radical cystectomy, even if T1
  - ***Nested variant***: rare; very aggressive
- ***MIBC = Muscle Invasive Bladder Cancer***
  - Invades into the muscularis propria or deeper (T2-T4)
- Tx: (in general; see later in chapter the Treatment section for more details)
  - NMIBC: TURBT, immediate post-TURBT Mitomycin C in select patients, intravesical BCG ± maintenance, and/or selective early radical cystectomy
  - MIBC: neoadjuvant chemotherapy (MVAC or ***gemcitabine & cisplatin***), radical cystectomy with pelvic lymph node dissection

SQUAMOUS CELL CARCINOMA (SQCC)

- Approximately 5% of bladder cancer in USA
- Most commonly found in the trigone, associated with ***9p*** and ***16p***
- **Bilharzial SqCC**: caused by ***Schistosoma haematobium***
  - Younger patients, lower incidence of metastasis
- **Non-Bilharzial SqCC**: caused by ***chronic irritation*** (i.e. chronic catheters, chronic UTI, bladder calculi)
  - Up to 5% of paraplegics with chronic catheters will have SqCC
  - Metastatic/invasive cervical SqCC
- Common for metastasis to ***bone***
- Urinary excretion of ***psoriasin***
- Prognosis is same for SqCC as same staged TCC
- Tx: same as TCC; neoadjuvant chemotherapy prior cystectomy for MIBC

ADENOCARCINOMA

- < 2% of bladder cancer in the USA
- **Primary vesical**
  - Usually at bladder dome / base in response to chronic inflammation
  - Mucin-producing and poorly differentiated

  - Signet ring adenocarcinomas may produce ***linitis plastica*** of the bladder
  - Most common associated bladder tumor with ***exstrophy***
- **Urachal**
  - Rare; located at bladder dome
  - One of the few indications for a ***partial cystectomy*** (bladder cancer within a diverticulum is another possible indication)
  - Dissection template:
    - Anterior: to include ***posterior rectus sheath***
    - Laterally: area between ***medial umbilical ligaments***
    - Superior: to include the ***umbilicus***
    - Inferior: ***bladder cuff*** of benign urothelium surrounding urachal attachment
- **Metastatic**
  - Gastrointestinal, endometrium, prostate, breast, ovary, cervical
- Tx: same as TCC, except all patients with adenocarcinoma need to ***rule out metastatic etiology*** (i.e. colonoscopy, PAP smear, breast exam, etc.)

SMALL CELL CARCINOMA (SCC)

- < 1% of all bladder cancer in the USA;
- Poorly differentiated neuroendocrine epithelial tumor that is very aggressive
- Immunohistochemistry: Neuron-specific Enolase, Synaptophysin, Serotonin, S-100, Chromogranin
- ***Chemotherapy is 1st line treatment (cisplatin, etoposide = VP-16),*** then radical cystectomy if responds
- Radiotherapy is reserved for symptomatic bone metastasis
- Five year survival rates of all stages combined is near 20%

| DIAGNOSIS / WORKUP |

- Most common symptom is intermittent ***painless hematuria*** in nearly 85% of patients
  - Hematuria is ≥ 3 RBCs/hpf in 2 of 3 properly collected urinalysis
- 2nd most common symptom is ***irritative voiding symptoms*** (i.e. frequency, urgency, dysuria), found in 20-30% of patients
  - Usually associated with CIS and muscle invasive TCC
- **Cystoscopy**
  - Approximate 90% sensitivity / specificity near 100%
- **Cytology**
  - Approximately 75% sensitivity for high grade / stage TCC or CIS; specificity up to 95%
  - Much lower for low grade / superficial TCC (30-40%)
- **FISH**
  - Approximate sensitivity 50-80%% / specificity 90%
  - If FISH positive, and negative cytology, CT urogram, and cystoscopy: proceed with random bladder biopsies
- **NMP22** (quantitative) **/ BladderChek** (qualitative)
  - Bladderchek sensitivity 55% / specificity 85%
- **BTA Trak** (quantitative) **/ BTA Stat** (qualitative)
- All patients suspected of bladder cancer or positive bladder biopsy need cystoscopy with ***bimanual exam*** and upper tract imaging (i.e. ***CT urogram*** or retrograde pyelogram if GFR < 60 mL/min)
  - If hydronephrosis with mass near orifice = cT2+
  - Palpable mass after TURBT = cT3
  - Fixed, palpable mass after TURBT = cT4
- **Upper tract** involvement in 2% early on in disease process and up to 20% late

TURBT: TRANSURETHRAL RESECTION OF BLADDER TUMOR

- Diagnostic and concurrent treatment
- Resect all visual bladder masses with deep muscle component

- If occluding ureteral orifice, resect with loop cautery (cut phase)
    - Stents are controversial, and likely not necessary
- Consider bipolar resection which decreases bleeding, need for transfusion, and obturator response
- If non-muscle invasive appearing, no bladder perforation or other contraindication, consider ***Mitomycin C*** post-TURBT within 24 hours, preferably within 6 hours
- If **diverticular tumor**, cup biopsy only because of high perforation rate
    - If T1 = partial cystectomy because by definition diverticula do not have a muscle layer present, so T1 may actually be invasive
- ***Restaging TURBT*** is required for all high grade and T1 lesions
    - Approximately 20-30% of patients are overstaged
    - 10-15% (if muscularis propria present) and up to 50% (if muscularis propria not present) are understaged
    - Approximately 25% will have residual disease, which is a risk factor for progression and recurrence
- ***Random biopsies*** are required for partial cystectomy or if cytology shows high grade TCC despite only low grade lesions on TURBT
- ***Prostate biopsies*** are required at the 5 and 7 o'clock position to rule out urethral involvement if considering a neobladder; high grade tumor in close proximity; TCC refractory to intravesical BCG; unidentified source of positive cytology
- **Bladder perforation** during TURBT
    - ***Intraperitoneal***: cystorrhaphy; however, some small injuries may be managed with Foley catheter drainage
    - ***Extraperitoneal***: Foley catheter drainage up to 14 days then consider cystogram; if continued urine leak, may continue Foley for one more week; however, if not healed by the 3rd week, proceed to cystorrhaphy
- Post-operative bladder pain is best managed with opioids, anticholinergics, and ketorolac

WORKUP FOR INVASIVE BLADDER CANCER

1. ***Chest x-ray*** (CT chest if any abnormalities on x-ray)

2. ***CT Urogram*** (evaluates upper tracts, lymph nodes and viscera)
3. ***Liver function tests*** (evaluate for liver / bone metastasis)
4. ***Bone scan***: only if bone pain or elevated alkaline phosphatase
5. ***Albumin***: hypoalbuminemia has ~ 20% more complications associated with radical cystectomy

| TCC TREATMENT |

RISK STRATIFICATION

- **Low Risk (50%)**
  - Low grade solitary, primary Ta tumor
    - Progression rate < 5% at 5 years
  - Single dose Mitomycin C after TURBT
  - TURBT alone and wait 3 months for cystoscopy
- **Intermediate Risk (35%)**
  - Recurrent or multifactorial low grade Ta/T1 low grade
    - Progression rate < 10% at 5 years
  - Single dose Mitomycin after TURBT
  - BCG for 6 weeks (especially multifocal) +/- maintenance
- **High Risk (15%)**
  - Any high grade tumor or CIS
    - Progression rate 25-50% at 5 years
  - Single dose Mitomycin after TURBT
  - BCG for 6 weeks (especially multifocal) with maintenance
  - Consider early (< 3 month) cystectomy

MITOMYCIN C

- Bioreductive alkylating agent
- ***Reduces recurrence*** absolutely 12-15% (25-50% relative reduction), but does not change progression

- Most common side effects: chemical cystitis and genital/palmer rash
  - Rarely causes retroperitoneal fibrosis if given with bladder perforation

VALRUBICIN (VALSTAR®)

- Anthracycline glycoside
- Indicated for CIS refractory to BCG and not adequate surgical candidate
- 18% disease free at 6 months with durable responses > 1 year
  - If failure, reconsider cystectomy

BACILLUS CALMETTE–GUÉRIN (BCG)

- Immunotherapy – exact mechanism of action unclear
  - T1-helper immune response (IL-2, IFN-gamma)
  - Involves neutrophils, T-cells, NK cells
- Start 2-6 weeks after TURBT for intermediate and high risk patients
- Weekly treatments for 6 weeks and maintenance (e.g. 3 weeks every 3 months for 3 years) – ***need at least 1 year of maintenance*** (high risk likely needs 3 years of maintenance)
  - If unable to tolerate, dose reduce to 10%
  - Overall BCG confers ~ 25% reduction in risk of NMIBC (Ta, T1, CIS) progression (~10% BCG vs. ~14% controls)
  - BCG confers 45% reduction in risk of CIS progression
    - BCG is superior to intravesical chemotherapy
- **Contraindications**: traumatic catheter, hematuria, UTI, immunosuppression, active autoimmune disease, known allergy to BCG
  - Reflux, positive PPD, remote history of treated Tuberculosis, prosthetic devices are not contraindications
- **Toxicity**: irritative symptoms (cystitis), malaise, hematuria
  - If symptoms persist > 48 hours, obtain urine culture
  - Tx: anticholinergics, Phenazopyridine, acetaminophen
- **BCG Reaction**: 25% of patients
  - Flu-like symptoms (fever, chills, myalgias)

  - Tx: steroids, acetaminophen
- **Serious BCG Reaction**: 5% of patients
  - Recurring or high fever (> 39.5°C) after 24 hours
  - Tx: 3-6 months of Isoniazid (if high resistance rate, add Rifampin, Ethambutol)
    - Note: efficacy of BCG is not effected by isoniazid (INH); however, fluoroquinolones may decrease efficacy
- **BCG Sepsis**: 0.5% of patients
  - Concern if serious BCG reaction with continued pyrexia
  - May be fatal
  - Rule out more common etiology – bacterial UTI (e.g. E. coli) with sepsis
  - Tx: 3-6 months Isoniazid, Rifampin, Ethambutol, steroids

INTRAVESICAL TREATMENT FAILURE

- If initially treated with a chemotherapy intravesical agent (e.g. Mitomycin, Thiotepa), the patient is still a candidate for BCG with same response rate as untreated patients; however, BCG failures are unlikely to respond to intravesical chemotherapy
- If patient fails BCG treatment, consider salvage BCG with a 30-50% response
- If patient fails 2 rounds of intravesical BCG, then the patient will likely need a radical cystectomy
- If patient refuses cystectomy or not adequate surgical candidate, consider radiation and salvage chemotherapy (MVAC or gemcitabine & cisplatin)

CYSTECTOMY WITH NEOADJUVANT CHEMOTHERAPY

NEOADJUVANT CHEMOTHERAPY

- Should be given to all patients prior cystectomy for MIBC, unless contraindication present
- Survival benefit: MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) = ***Gemcitabine, Cisplatin***

  - ***Carboplatin***: substitute for cisplatin if renal insufficiency
- Toxicity: MVAC has greater toxicity
- Increased complete pathologic response (~ 33% vs. ~ 15%)
- Decreased mortality risk (~ 15%)

CYSTECTOMY WITH PELVIC LYMPH NODE DISSECTION

- Treatment of choice for MIBC (T2-T4); may consider if lymph node involvement
- Men: radical cystoprostatectomy
  - Urethrectomy if prostatic stromal TCC invasion
- Women: radical cystectomy, hysterectomy, and resection of the anterior vaginal wall
  - Urethrectomy if not constructing an orthotopic neobladder; tumor at the bladder neck
- Overall recurrence-free survival is ~ 65% at 5 and 10 years; up to 85-90% for pTa and pTis with negative lymph nodes
- Contraindication to cystectomy: distant metastatic disease (M1)
- See next section in this chapter for Conduits / Neobladders
- **Pelvic Lymph Node Dissection (PLND)**
  - ***Lymph nodes spread***: external/common iliac, obturator nodes, presacral, perivesical, inferior para-aortic
  - ***≥ 9 lymph nodes are required for adequate lymph node analysis***

BLADDER CANCER PLND TEMPLATES

Extent	Standard	Extended*
Proximal	Midportion of common iliac artery or aortic bifurcation	Inferior mesenteric artery
Medial	Bladder wall	Bladder wall
Lateral	Genitofemoral nerve	Genitofemoral nerve
Distal	Inguinal ligament	Inguinal ligament
Inferior	Pelvic floor	Pelvic floor

** Increased survival in both node positive and negative disease*

EARLY / IMMEDIATE CYSTECTOMY INDICATIONS

- ***High risk disease*** (high grade Ta, T1, CIS) particular in younger patients and/or ***BCG failures***

High Risk Non-Muscle Invasive Bladder Cancer

~ 85% of progression to muscle invasive bladder will occur within 48 months

- ***Multifocal***, high grade T1 disease
- ***Unfavorable histology*** (micropapillary TCC, SCC, SqCC, adenocarcinoma)
    - o Neoadjuvant cisplatin/ etoposide is required for small cell carcinoma
    - o If urachal adenocarcinoma, may consider partial cystectomy
- ***Lymphovascular invasion*** in T1
- ***Prostatic stromal TCC invasion*** (technically T4a disease; consider urethrectomy)
- ***Bladder cripple with recurrent disease***
- High grade T1 in ***diverticulum*** (consider partial cystectomy)

HIGH RISK NMIBC CYSTECTOMY TIMING AND SURVIVAL

Cystectomy Timing	5-year CSS	10-year CSS
Immediate (< 3 months)	~ 80%	~ 75%
Delayed	~ 70%	~ 50%

CSS = cancer specific survival

| PROGNOSIS |

- Factors associated with recurrence / progression
- Grade
- Concomitant CIS
    - If untreated, ~50% progresses to MIBC in 5 years
- Stage
- Others factors:
    - Tumor presence at initial 3 month cystoscopy
    - Prior recurrence
        - T1 or CIS has 5-7% progression per year
    - Multifocality
        - Single vs. 2-7 tumors vs. > 8 tumor
    - Tumor size > 3cm

SURVEILLANCE

- TCC is the most expensive cancer to treat/survey on a per patient basis
- Surveillance timing is variable and controversial depending on the grade/stage

BLADDER CANCER SURVEILLANCE

Method	Low Risk	Intermediate Risk	High Risk
Cystoscopy*	Quarterly x 1 yr ⇨annually	Quarterly x 2 yrs ⇨ semiannually x 2 yrs ⇨ annually	Quarterly x 2 yrs ⇨ semiannually x 2 yrs ⇨ annually
Cytology	None (if initially negative)	With every cysto	With every cysto
Upper Tract	None (if initially negative)	Biennial	Annual

** If positive: re-risk stratify, and restart surveillance timing*

NEOPLASTIC PATTERNS

- Approximately 75% of initial diagnosis is superficial (Ta/T1) with 20% progressing to muscle invasive; 30% present initially as muscle invasive (T2+); 5% present with metastatic disease
- ***Prostatic involvement*** is seen in over 40% of radical cystectomy specimens by muscle invasive TCC
    - ***Prostatic stroma*** is the key to clinically significant involvement, which is associated with high prevalence for distant metastasis
- Approximately 10% of all radical cystectomies have no identifiable tumor found (pT0)
- If metastatic disease, nearly all patients have muscle invasive TCC
- **Hematogenous spread**: liver, lung, bone, adrenal glands, intestine

PREVENTION

- High fat / cholesterol diets have increased risk
- High fluid intake has decreased risk
- COX-2 inhibitors may prevent recurrence
- Quit smoking at any point will reduce recurrence / progression

| METABOLIC DISTURBANCES ASSOCIATED WITH CONDUITS / NEOBLADDERS |

CONDUITS

METABOLIC DISTURBANCES

- ***Stomach***: hypokalemic, hypochloremic, metabolic alkalosis
- ***Jejunum***: hyponatremic, hyperkalemic, hypochloremic, metabolic acidosis
- ***Ileum / Colon***: hypokalemic, hyperchloremic, metabolic acidosis (colon related hypokalemia is worse than ileum)
    - o Tx: (1st line) potassium citrate, sodium citrate or citric acid solution
        - * Increases citrate, which is moved into mitochondria during intracellular acidosis, allowing for pH to rise
    - o Tx: (2nd line) chlorpromazine or nicotinic acid
        - * Inhibits chloride transport, thus decreasing bicarbonate loss
    - o Creatinine, urea, osmotic contents may all be absorbed by the ileal conduit

SIDE EFFECTS

- ***Diarrhea – ileum / colon mostly***
    - o Bile salts, which emulsify fats, are usually reabsorbed at the terminal ileum. These salts are irritative to the colon causing diarrhea and steatorrhea from decreased fat emulsification
    - o Tx: Cholestyramine, high bulking fiber diet, Loperamide
- ***Hypocalcemia / Osteomalacia***
    - o Renal wasting and acidosis being buffered via calcium resorption from bone, and may lead to demineralization
    - o Sx: tetany, paresthesias, QT prolongation
    - o Tx: Vitamin D and Calcium supplementation, Potassium citrate

to decrease acidosis

- ***B12 deficiency*** – ileum (B12 absorption), stomach (intrinsic factor)
    - Absorbed in the terminal ileum with body stores up to 3-5 years
    - May lead to megaloblastic macrocytic anemia and neurologic deficits
    - Tx: B12 supplementation – oral vs. intramuscular
- ***Elevated medications levels***: methotrexate, phenytoin, lithium, theophylline, several antibiotics

SUMMARY OF METABOLIC DISTURBANCES WITH CONDUITS

Bowel	Sodium	Potassium	Chloride	Metabolic
Stomach	---	↓	↓	Alkalosis
Jejunum	↓	↑	↓	Acidosis
Ileum / Colon	---	↓	↑	Acidosis

** NOTE: each conduit has only one elevation and no other conduit shares it (i.e. stomach – pH, jejunum – potassium, Ileum / Colon – chloride)*

NEOBLADDERS

- **Mainz pouch** = ileocolic pouch
    - Division of the ***right colic*** will increase mobilization if needed and the ***Arc of Drummond*** will maintain arterial supply to the remaining colon.
- **Hautmann** = W pouch from distal ileum
- **Ghoneim** = Hautmann with extramural tunnel for ureters
- **Studer** = distal ileum ball with long afferent limb
- Avoid neobladders in patients with Cr > 2 (chronic renal failure), hepatic failure, and Crohn's disease
- Incontinence risk factors: short urethral length, non-nerve sparing, extrinsic sphincter injury, unable to time void (lack of fullness sensation)
    - ***Daytime stress incontinence***: reduced outlet resistance with decreased compliance / capacity (Tx: timed voids, urethral bulking agents, urethral sling, or artificial urinary sphincter)

        - Observe incontinence for up to a year to allow for increased capacity / compliance prior to surgery
    - ***Nighttime stress incontinence***: increased volume accumulated in neobladder while sleeping and lack of sensation (Tx: timed voids, CIC)
        - If late onset, secondary to ***mucous plugging*** causing retention

MISCELLANEOUS

- ***Bricker anastomosis***: end (ureter) to side (bowel); 2 separate anastomoses
- ***Wallace anastomosis***: ureters Y-anastomosis together then end (ureter) to end (bowel)

Anastomosis Mnemonic

Bricker, both ureters have anastomosis to bowel

Wallace, one ureteral anastomosis to bowel

- ***Avascular plane of Treves***: avascular region between the ileocolic artery and SMA terminal branches
    - Defines the distal end of ilium used for conduits and orthotopic neobladders, and allows for appropriate mobilization
- ***Urinary leak within abdomen / pelvis***
    - Immediate: secondary to non-water tight neoureterostomy
        - Tx: maintain stents and JP drain
    - Late: secondary to ischemia or necrosis
        - Tx: percutaneous drain and stomal catheter; if unresolved then reoperation in future
- ***Prior pelvic radiation*** is now only a relative contraindication. Classically if a patient had pelvic radiation, then use transverse colon only; however, currently the surgeon may evaluate the intestinal tissue and make intraoperative decision to utilize the distal ileum
- Non-refluxing ureterointestinal anastomoses prevents increased

upper tract pressure; however, it does not decrease bacterial colonization of the upper tract!

- ***Dusky stoma***: immediately after surgery, it is common to be dusky; however, if persists for a few days, consider ***loop endoscopy*** to define level of ischemia
    - Most common etiology = surgical technique (i.e. tension causing thrombosis, mesentery hematoma, or inadequate blood supply)
- ***Fistula***: if fistula forms between neobladder / conduit and intestines the treatment is based on symptoms and abdominal contamination
    - Asymptomatic = conservative, bowel rest, observation
    - Symptomatic / No contamination = primary repair
    - Symptomatic / Contamination = proximal loop ostomy with secondary repair at later date
- ***Parastomal hernia***
    - Primary: repair in situ with mesh
    - Recurrent: relocate stoma to opposite side of the abdomen
- ***Urethrectomy at time of radical cystectomy***
    - Men: prostatic stromal TCC
    - Women: bladder neck TCC
    - May consider in all patients with cutaneous diversions, as up to 10% may have urethral TCC in the future
- ***Urethral TCC following cystoprostatectomy***
    - Urethral wash cytology may be beneficial for early diagnosis, particularly in orthotopic diversions (not beneficial in primary urethral carcinoma)

CHAPTER 9: PROSTATE CANCER

- Vast majority (~95%) of prostate cancer histology is ***adenocarcinoma***, and majority (~70%) is found in the ***peripheral zone*** and formed from ***epithelial cells***.

EPIDEMIOLOGY

- In the USA, 1 in 6 men are diagnosed with prostate cancer (CaP) in their lifetime
- In the USA, 1 in 6 men diagnosed with CaP will die from it (overall, ~ 3% of American men die from CaP)
- Most common non-cutaneous cancer in men, and 2nd most common cause of male death from cancer
- Almost 50% of men > 70 have incidental CaP

PROSTATE SPECIFIC ANTIGEN (PSA)

- Aka Kallikrein-3
- PSA is a serine protease secreted from prostatic acinar epithelial cells and liquefies semen
- t1/2 = 2-3 days
- PSA levels are higher with advanced age, prostate volume / BPH, African-Americans, elevated testosterone levels, prostatic infections, and prostate cancer

REFERENCE RANGES OF AGE & RACE RELATED PSA (NG/ML)*

Age	Whites	Blacks
40-49	0-2.5	0-2
50-59	0-3.5	0-4
60-69	0-4.5	0-4.5
70-79	0-6.5	0-5.5

** If hypogonadal male, the PSA will likely be less than normal; therefore, if PSA is in normal reference range, consider prostate biopsy prior hypogonadal treatment.*

- **Total PSA = free PSA + bound (complex) PSA**
  - ***Free/Total PSA Ratio***: only indicated for PSA 4-10; increases specificity
  - Free PSA may transiently be elevated after cystoscopy, vigorous prostate massage, infection, catheterization, prostate biopsy
  - PSA binds to ***antichymotrypsin*** and ***alpha-1 macroglobulin***
  - Total PSA is unchanged by hemo- / peritoneal dialysis; however, free PSA is altered by hemodialysis

"Bound is Bad"

Bound PSA is elevated in prostate cancer, particularly for PSA 4-10 (i.e. the higher % free PSA, the lower probability of CaP)

- **PSA Doubling Time**
  - PSA doubling time ≤ 10 months is an ominous sign
- **PSA Velocity**
  - Need at least 3 PSA values over ≥ 18 months
  - PSA velocity ≥ 0.35 ng/ml/year with a PSA < 4 is concerning
  - PSA velocity ≥ 0.75 ng/ml/year with a PSA 4-10 is concerning

- **PSA Density**
    - PSA / prostate volume
    - > 0.15 is concerning
- U.S. Preventive Services Task Force recommends against PSA screening for prostate cancer

AUA PSA RECOMMENDATIONS

Age	Recommendation*
< 40	Do not screen
40-54 (Average risk)	Do not screen
40-54 (High risk)	Patient-doctor decision
55-69	Patient-doctor decision
> 70	Do not screen

** Caveats: do not screen patients with a life expectancy < 10-15 years; may consider biennial screening*

- NOTE: ~ 90% of CaP is now diagnosed as clinically, localized disease due to screening
- ***Baseline (45-49 year old) PSA ≥ 0.7ng/mL confers to a higher risk for prostate cancer, and may consider annual screening***
- PSA > 50 ng/mL has a 98.5% positive predictive value of prostate cancer
- If hypogonadal patient is on ***testosterone replacement therapy*** (TRT), stop therapy and biopsy for any of the following:
    - PSA increases > 1.4 ng/mL
    - PSA velocity > desired threshold (e.g. ≥ 0.35 or 0.75 ng/mL/year)
    - Abnormal DRE

PROSTATE BIOPSY

- Transrectal ultrasound with 12 core prostate biopsy is standard
  - ~ 1/3 more cancers detected than tradition 6 core biopsy
  - Transrectal approach has ~ 2% post-biopsy infection / sepsis
  - ***Transrectal ultrasound alone has no role in prostate cancer detection***
  - On repeat biopsy, consider ***anterior apical horn*** biopsy
- Saturation/Extended biopsy indications
  - At least 2 negative 12 core prostate biopsy despite continue PSA increase
  - Provide more accurate staging, especially for active surveillance patients
- Transperineal stereotactic template-guided saturation prostate
  - More precise and accurate than the traditional saturation biopsy
  - Apical and anterior prostate is more easily biopsied transperineal
  - Transperineal approach has near 0% post-biopsy infection/ sepsis

PERCENTAGE OF PROSTATE CANCER PER ZONE*

Zone	Percent of CaP
Peripheral	70%
Transitional	20%
Central	10%

**Approximate values to aid in memory*

- **High-grade Prostatic Intraepithelial Neoplasia (HGPIN)**
  - Severe dysplasia, but still maintains an intact basement membrane
  - 80/20 Rule: ~ 80% of all prostate cancer have HGPIN; ~ 20% of patients with HGPIN (without CaP currently) will be diagnosed with CaP

        - * Number of cores (volume) is more predictive than its presence
    - *1 core HGPIN*: re-biopsy ***in 3 years***
    - *2+ core HGPIN*: re-biopsy ***within 1 year***
- **Atypical Small Acinar Proliferation (ASAP)**
    - Re-biopsy in ***3-6 months***
    - ~ 40% of these patients have prostate cancer on re-biopsy
- **Atypical Adenomatous Hyperplasia**
    - Benign; not an indication for re-biopsy
- ***Prostate ductal adenocarcinoma*** is automatically Gleason 4+4 = 8 (cribriform), and have higher recurrence rates

PROSTATE CANCER HISTOLOGICAL STAINS

- **AMACR** = Alpha-methylacyl-CoA racemase (over-expressed in CaP and papillary RCC)
- **HMWCK** = high-molecular-weight cytokeratin (***34-beta-E12***) - present in normal prostatic basement membrane
    - Note: positive stain in bladder TCC and collecting duct RCC
- **PAP** = prostatic acid phosphatase (over-expressed in CaP)
- **PSA** = prostate surface antigen (identifies prostatic tissue)

WORK UP

- **Bone Scan**: Usually reserved for patients with diagnosed prostate cancer and a PSA > 20; however, may be considered in all high risk categorized patients
    - Consider if bone pain and/or elevated alkaline phosphatase

PSA AND RISK OF METASTASIS*

PSA	Lymph Node Metastasis	Bone Metastasis
≤ 10	5%	2%
10 - 20	20%	5%
> 20	35%	15%

* *Numbers are approximated to aid in memory*

- **CT Scan**: Consider in high risk categorized patients
- **MRI**: not superior to CT scanning for identifying lymph node metastasis.
    - o Endorectal coils may have a role in identifying local extension
- **11C-choline PET Scan**
    - o Uptake does not differentiate between BPH and CaP
    - o ***Indicated: biochemical recurrence*** after previous CaP treatment
    - o Reasonably high false positive rate, so biopsy tissue with abnormal PET

TNM/STAGING POINTS

- ***T1 disease is not palpable on digital rectal exam (DRE), nor visualized on transrectal ultrasound (TRUS)*** - i.e. it is found incidentally on TURP or elevated PSA
    - o Example: if DRE / TRUS negative and biopsy positive in bilateral lobes, its still only T1c
- ***T2 disease is either palpable on DRE or visualized on TRUS***
    - o T2a: < ½ of single lobe
    - o T2b: > ½ of single lobe
    - o T2c: any amount in both lobes
- T3: extraprostatic extension (T3a), or seminal vesicles (T3b)
- T4: involves surrounding organs

- Mets: distant nodes (M1a), bone (M1b), other (M1c)
    - NOTE: T1*b* = ***bone***
- For detailed staging information: http://www.cancer.net/cancer-types/prostate-cancer/staging-illustrations

D'AMICO PROSTATE CANCER RISK CATEGORIES

	Low Risk	**Intermediate Risk**	**High Risk**
PSA	≤ 10	10 – 20	< 20
Gleason Score	≤ 6	7	≥ 8
TNM Stage	≤ T2a	T2b	≥ T2c

LOCALIZED PROSTATE CANCER

- ***Defined as T1-2, N0, M0***
- Although somewhat controversial, the number needed to treat (NNT) in prostate cancer is likely around 12 (Goteborg Screening Trial and ERSPC) once followed out far enough (> 10-12 years)
    - Original ERSPC data (taken out only 9 years) showed number needed to screen was 1410, and NNT was 48.

LOCALLY ADVANCED PROSTATE CANCER

- ***Defined as T3-4, N0-1, M0***
    - Increased risk of progression and death without treatment
- Risk factors for locally advanced prostate cancer (CaP): high serum PSA and Gleason score, perineural invasion, lymphovascular invasion, ductal or neuroendocrine differentiation, high number / volume of positive biopsy scores
- Clinical T3 disease: prior to treatment, aware of T3 disease
- Pathologic T3 disease: prior to treatment, thought to be < T3 disease

| HORMONE SENSITIVE PROSTATE CANCER TREATMENTS |

ACTIVE SURVEILLANCE

- This is a patient-driven form of ***delayed treatment*** with ***active monitor for disease progression***
    - This is different from watchful waiting, which does not involve monitoring, only possible palliation of metastatic disease
- Unclear exactly who is the best candidate for active surveillance; however, consider patients predicted to live < 10 years, low grade disease, low volume cancer, and organ confined disease.
- Pro: decrease overtreatment of insignificant prostate cancer, and avoid associated side effects
- Cons: may miss window to cure / nerve spare, multiple prostate biopsies, anxiety, can not assure indolent nature of tumor
- Surveillance: ***DRE / PSA every 6 months, Prostate biopsy every year***
    - PSA velocity > 0.35 ng/mL/year is ominous sign

Indications to Progress from Active Surveillance to Treatment

Gleason pattern ≥ 4 present,

≥ 3 positive biopsy cores, or

> 50% of a biopsy core is positive

RADICAL PROSTATECTOMY

LOCALIZED PROSTATE CANCER (T1-2, N0, M0)

- ***Gold standard for localized CaP***
- Options: open, perineal, laparoscopic, robotic; salvage ("secondary treatment")
- Pro: potential cure, more accurate staging
- Cons: potential side effects (e.g. urinary incontinence, erectile dysfunction), major surgery
    - If patient complains of urinary incontinence and not reproducible on urinary dynamics, remove Foley and valsalva with a full bladder. He likely has anastomotic stricture and stress urinary incontinence (i.e. the Foley was occluding the urethra at the site of the stricture)
- ~ 75 years old is the upper age limit to offer a radical prostatectomy
- Neoadjuvant ADT is unhelpful, and may increase surgical difficulty
- ***Expect post-prostatectomy PSA to nadir < 0.2 ng/mL***
    - ≤ 0.1 is considered undetectable
    - If PSA > 0.2 ng/mL will need to consider radiation therapy and/or androgen deprivation therapy
    - ~ 1/3 will have biochemical recurrence (~2/3 with high risk pathologic features will have biochemical recurrence)
        - 50% of post-radical prostatectomy patients with biochemical recurrence will die from prostate cancer

LOCALLY ADVANCED PROSTATE CANCER (T3-4, N0-1, M0)

- Select patients with clinically, local, advanced CaP (T3 disease) benefit from a prostatectomy, but will likely need adjuvant treatment
    - Neoadjuvant androgen ablation is not indicated prior prostatectomy
- Post-prostatectomy (pathologic) findings of local spread: positive surgical margin, seminal vesical involvement (SVI), extracapsular extension (ECE), lymph node involvement
    - ***Adjuvant*** (immediate with PSA < 0.2) ***radiation treatment is***

superior to salvage (delayed; PSA was never < 0.2 or was < 0.2 then started to rise) ***radiation treatment if positive surgical margin, SVI or ECE***

- EORTC 22911, SWOG 8794
- ~ 40% of patients with positive surgical margins will have biochemical recurrence
- ***If salvage XRT, start treatment while PSA ≤ 0.5 ng/mL*** (48% vs. 28% progression-free survival at 6 years)

TUMOR EXTENSION AFFECT ON POST-PROSTATECTOMY PSA-FREE SURVIVAL*

Pathologic Involvement	**5 year Biochemical Recurrence-Free Survival**
Organ confined	95%
Extracapsular extension	75%
Seminal vesicle involvement	35%
Lymph node involvement	20%

* *Values approximated*

Post-Prostatectomy Recurrence

PSA ≥ 0.2 ng/mL

(≤ 0.1 is considered undetectable)

- **Salvage Prostatectomy**
  - Radical prostatectomy after patient fails radiation or cryotherapy
  - Much more difficult operation with greater complication rates of urinary incontinence, erectile dysfunction, and bladder neck contracture

- **Pelvic Lymph Node Dissection (PLND)**
    - Indicated for patients in the intermediate to high risk categories
    - PLND is not therapeutic, rather diagnostic to guide treatment

Lymph Node Involvement (N1) found on PLND

Immediate and lifetime ADT (ECOG 3807)

- Median time from post-prostatectomy PSA failure to metastases: 8 years
- Median time from metastases to death: 5 years
- Therefore, cancer-specific mortality averages 13 years

ANDROGEN DEPRIVATION THERAPY (ADT)

LOCALIZED PROSTATE CANCER (T1-2, N0, M0)

- ADT used alone is not indicated for localized prostate cancer because the side effects out way the benefits (e.g. cardiac disease, diabetes mellitus)

LOCALLY ADVANCED PROSTATE CANCER (T3-4, N0-1, M0)

- Not a curative treatment; however, may offer long term remission
- Early adjuvant androgen deprivation therapy (ADT) may be beneficial in ***high risk*** patients with pT3 disease (avoid in low risk patients)
- Intermittent ADT may be an option in some patients, and increase their quality of life
- If PSA rises while on ADT, ***check testosterone*** to assure ***< 50*** (traditionally); evidence that lower the better (< 20)
    - If > 50, consider orchiectomy or abiraterone
    - If < 50, start / stop Bicalutamide (opposite of current treatment)

METASTATIC PROSTATE CANCER (Tany, Nany, M1-2)

- Indefinite ADT is recommended
- Once bone metastasis, increase bone protective treatment
  - Zoledronic Acid 4mg every 4 weeks (if creatinine clearance > 60 mL/min)
  - Denosumab (Xgeva®) 120mg every 4 weeks

Androgen Deprivation Therapy

Once the patient is refractory to ADT (i.e. PSA rise while on ADT), continue ADT indefinitely to prevent sudden, severe cancer flare

ADT METHODS

- **Gonadotropin-releasing hormone (GnRH) *agonist***
  - Continuous GnRH stimulation leads to initial transient androgen elevation followed by pituitary suppression that results in castration androgen levels in approximately 21-28 days
  - ***GnRH agonist*** is associated with transient, testosterone ***flare phenomenon*** (stimulation of LH results in increased testosterone, thus flare of prostate cancer during initiation of treatment; may suppress with anti-androgen)
  - Side effects: decreased libido, erectile dysfunction, hot flashes, fatigue, weight gain, loss of muscle mass, gynecomastia, breast tenderness, testicular atrophy, bone demineralization, diabetes, cardiovascular disease, QT prolongation, cognitive decline, metabolic syndrome, anemia
    - Bothersome hot flashes may be treated with Megestrol acetate or Diethylstilbestrol; however, may also lead to further side effects
  - **Leuprolide** (Lupron®, Eligard ®)
    - Dose: 7.5mg monthly, 22.5mg every 12 weeks, 30mg every 16 weeks, 45mg every 24 weeks (Lupron-IM, Eligard-subcutaneous)

- o **Triptorelin** (Trelstar®)
    - * 3.75mg IM every 4 weeks, 11.25mg IM every 12 weeks, or 22.5mg IM every 24 weeks
- o **Goserelin** (Zoladex®)
    - * 10.8mg subcutaneously every 12 weeks (or 3.6mg every 28 days)

- **GnRH *antagonist***
    - o No flare phenomenon with antagonist of GnRH
    - o **Degarelix** (Firmagon®)
        - * Initially 240mg subcutaneously the 1st month, followed by 80mg every 28 days
        - * Side effects: injection site reaction, hot flash, weight gain, elevated liver enzymes, QT prolongation, decreased libido, gynecomastia, osteoporosis
    - o **Abarelix** (Plenaxis®)
        - * Indicated for palliative treatment when LHRH agonist is contraindicated and patient refuses orchiectomy with either neurologic compromise from metastatic CaP, obstructive uropathy, or intractable pain from bone metastasis
        - * Black Box Warning: immediate onset of systemic allergic reactions (hypotension / syncope), anaphylaxis
        - * No data on effectiveness beyond 12 months of treatment
- **Non-steroidal Anti-Androgen**
    - o Competitively inhibits androgens from binding androgen receptors
    - o Non-steroidal anti-androgens are not adequate for prostate cancer alone. In fact, when given alone they increase LH and testosterone
    - o These medications are particularly helpful to suppress the ***flare phenomenon*** seen when initially starting GnRH / LHRH agonists
    - o These medications may be ***added / withdrawn from androgen deprivation regimens as PSA rises*** (e.g. if on GnRH agonist and anti-androgen with PSA rise, remove the anti-androgen; if

on GnRH agonist only with PSA rise, add an anti-androgen)

  - o **Bicalutamide** (Casodex®): 50mg daily in combination with GnRH agonist
  - o **Flutamide** (Eulexin®): 250mg every 8 hours in combination with GnRH agonist
  - o **Nilutamide** (Nilandron®): 300mg daily for 1 month, then 150mg daily in combination with bilateral orchiectomy
    - * Improved survival vs. orchiectomy + placebo (27.3 vs. 23.6 months)
  - o Side effects: ***hepatotoxicity***, gynecomastia, breast pain, glucose intolerance, diarrhea (especially Flutamide), night vision blindness (Nilutamide)
- **Bilateral orchiectomy**: castration levels within 24 hours

OSTEOPOROSIS ASSOCIATED WITH ADT

- **DEXA scan** (Dual energy x-ray absorptiometry)
  - o Obtain baseline prior to starting ADT, then DEXA scans every 1-2 years
- Bone loss may begin as early as 6 months on ADT
- **Behavioral changes**: smoking cessation, weight bearing exercise
- **Vitamin D** (800-1,000 IU) **and Calcium** (1,200 mg) supplementation daily
  - o Serum 25-hydroxycholecalciferol goal:
    - * > 30 ng/mL (National Osteoporosis Foundation)
    - * > 20 ng/mL (US Institute of Medicine)
- Treat osteoporosis (T score < -2.5) and osteopenia (T score -1 to -2.5)
- The **T-score** is the standard deviation below the reference mean, which is a 30 year old, healthy adult of the same gender and race.
  - o The **Z-score** is the standard deviation below or above the average expected for a patient of the same age, weight and race.
    - * Z-score < -2 is abnormal
- **Zoledronic acid** (Reclast®)
  - o Bisphosphonate; Inhibits the mevalonate pathway reducing

osteoclast activity
  - 5mg annually
  - Must be renal dosed and administered intravenously
  - Side effects: musculoskeletal pain, flu-like symptoms, osteonecrosis of the jaw
- **Alendronate** (Fosamax®)
  - Bisphosphonate; inhibits osteoclasts
  - 70mg weekly or 10mg daily
- **Denosumab** (Prolia®)
  - Binds to RANK Ligand to inhibit osteoclast formation and function
  - 60mg every 6 months
  - Not renal doses and administered subcutaneously
  - Side effects: musculoskeletal pain, hypocalcemia, osteonecrosis of the jaw

RADIATION THERAPY

- **PSA Bounce** = rise in PSA following radiotherapy with quick return to pre-bounce levels
  - ~ 12% of XRT, ~ 33% of brachytherapy
  - Usually does not rise > 2-3 ng/mL
  - Usually occurs within 3 years of radiation treatment

LOCALIZED PROSTATE CANCER (T1-2, N0, M0)

- **Permanent brachytherapy ("seeds")**
  - Iodine-125 half-life = ***60 days***
  - Palladium-103 half-life = 17 days
  - Lower urinary tract voiding symptoms is common for 4-5 half-lives
    - Usually responds to ***alpha-blockers***; if not, then ***CIC / Foley***

- Urinary retention is most commonly seen in higher IPSS scores and larger prostates
- **TURP** needed in ~ 5%; wait until after 3 months from insertion of brachytherapy
    - Limit resection and preserve the apical tissue
    - Increased urinary incontinence (up to 20%)!!!
- **TUMT** is contraindicated after brachytherapy

Brachytherapy – Excellent Implant

≥ 90% of the prostate receives at least 100% of the prescribed dose

- **High dose rate brachytherapy (HDR)**
    - May be administered with co-current XRT
- **External beam radiation therapy (XRT)**
    - Consider ADT based on risk category
    - 3D conformal radiation treatment (3D-CRT) and Intensity-modulated radiation therapy (IMRT) are more modern delivery methods of radiation

PRIMARY XRT WITH CONCURRENT ADT: BASED ON RISK GROUP*

Prostate Cancer Risk Group	ADT Treatment Time
Low	None
Intermediate	6 months
High	2-3 years

* *Start ADT therapy 8 weeks prior the start of XRT*

- **Post-radiation Recurrence**
    - **ASTRO Criteria**: 3 consecutive PSA rises
        - Recurrence date: midpoint between last undetectable PSA and the 1st of the three consecutive rises
    - **Phoenix criteria**: PSA nadir + 2

LOCALLY ADVANCED PROSTATE CANCER (T3-4, N0-1, M0)

- **Permanent brachytherapy**
    - Traditionally used only in lower risk and localized CaP
- **High dose rate brachytherapy**
    - Increased benefit when combined with XRT (initial treatment)
- **External beam radiation therapy (XRT)**
    - May be primary, adjuvant or salvage treatment
    - Traditionally, clinically T3 disease favors primary XRT (trend to consider prostatectomy in these patients with adjuvant XRT as needed)

Post-Radiation Recurrence

ASTRO Criteria: 3 consecutive PSA rises

Phoenix criteria: PSA nadir + 2

CRYOABLATION

LOCALIZED PROSTATE CANCER (T1-2, N0, M0)

- Active / rapid ***freeze via Argon***, and active ***thaw via Helium***
    - Requires 2 freeze-thaw cycles for best results (passive thaw better, but time consuming)
    - Freeze the entire prostate to - 40°C
    - Neurovascular bundle, Denonvilliers' fascia, and external sphincter temperature probes
- Indications:

  - **Initial treatment** for low risk / localized prostate cancer
  - **Salvage treatment** for patients that failed radiation therapy with localized disease
- Contraindications: previous TURP (relative)
- Side effects: very high ***erectile dysfunction*** rates
- Focal cryotherapy is not currently recommended, but offers potentially less side effects

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

LOCALIZED PROSTATE CANCER (T1-2, N0, M0)

- Not FDA approved for prostate cancer treatment at the time of writing this chapter
- Utilizes ultrasound to generate heat that causes necrosis

| CASTRATE-RESISTANT PROSTATE CANCER (CRPC) |

- Defined as ***prostate cancer progression despite adequate testosterone suppression***
  - May be nonmetastatic, which will eventually progress to metastatic disease
- ***Androgen deprivation therapy is continued indefinitely*** once castrate-resistant, despite cancer progression, as increased testosterone may exacerbate the progression
- Metastatic disease may develop ***obstructive uropathy*** that requires ureteral stents or percutaneous nephrostomies

PRE-CHEMOTHERAPY TREATMENT OPTIONS

- **Sipuleucel-T** (Provenge®): immunotherapy
  - Autologous CD54+ dendritic cells are activated with recombinant prostate acid phosphatase and granulocyte-macrophage colony-stimulating factor; this stimulates T cell production of interleukins (i.e. cytokines)

    - Administered a total of 3 doses at 2 week intervals between each dose
  - Indication: ***asymptomatic or minimally symptomatic CRPC***
  - Overall median survival 25.8 months (Sipuleucel-T) vs. 21.7 months (control) - IMPACT Trial
  - Side effects: flu-like symptoms (most common) secondary to cytokine release; acute infusion reactions
    - Tx: premedicate with Acetaminophen and antihistamine
- **Abiraterone acetate** (Zytiga®): androgen biosynthesis inhibitor
  - ***CYP 17 inhibitor (17-alpha-hydroxylase / 17,20-lyase), which decrease overall body androgen levels***
    - Inhibits androgen production by testicles, adrenals and prostate cancer cells
  - 1,000mg daily on an empty stomach with prednisone 5mg BID
  - Indication: pre- or post-chemotherapy for metastatic CRPC
  - Increased median time to chemotherapy treatment vs. placebo (25.2 vs. 16.8 months); increased radiographic progression-free survival (abiraterone has not reached median, but is significant with HR = 0.425); overall survival trended (not significant) better than placebo (35.3 vs. 30.1 months)
  - Side effects: ***HTN, hypokalemia and fluid retention*** (aldosterone excess); adrenal insufficiency; ***hepatotoxicity***; fatigue, edema, hot flash, GI upset
    - Monitor ALT, AST, and bilirubin at baseline, every 2 weeks for the first 3 months, then monthly

CHEMOTHERAPY

- **Docetaxel**: Taxane
  - Drug of choice for ***metastatic CRPC*** treatment
  - Microtubule stabilization and allows apoptosis that is lost in CaP
  - Superior to Mitoxantrone (overall survival: 18.9 vs. 16.4 months; TAX 327 study)
  - Side effects: myelosuppression, fatigue, neurotoxicity, hyperlacrimation, edema, liver dysfunction

- **Cabazitaxel**: Taxane
  - 2nd line chemotherapy for metastatic CRPC, if progression during / after docetaxel
  - TROPIC trial: overall survival of cabazitaxel 15.1 months vs. mitoxantrone 12.7 months; also increased progression-free survival
  - Side effects: myelosuppression (neutropenia), diarrhea, fatigue, peripheral neuropathy
- **Mitoxantrone**:
  - Chemotherapy for palliation of symptoms from metastasis

Prostate Adenocarcinoma Chemotherapy

Docetaxel – 1st line

Cabazitaxel – 2nd line

POST-CHEMOTHERAPY TREATMENT OPTIONS

- **Abiraterone acetate** (Zytiga®): androgen biosynthesis inhibitor
  - ***CYP 17 inhibitor (17-alpha-hydroxylase / 17,20-lyase), which decrease overall body androgen levels***
  - Overall survival benefit post-chemotherapy vs. placebo (15.8 vs. 11.2 months)
  - See pre-chemotherapy setting for further medication details
- **Enzalutamide** (Xtandi®; formerly MDV3100): androgen receptor modulator
  - Inhibits androgen binding to androgen receptors (most importantly, testosterone-sensitive prostate cancer cells); inhibits androgen receptor nuclear translocation; and inhibits DNA binding and activation of androgen receptors
  - 160mg daily
  - AFFIRM trial showed improved overall survival vs. placebo (18.4 vs. 13.6 months); also significant reduction of PSA by > 50%; increased time to PSA progression (8.3 vs. 3.0 months)

      - PREVAIL trial is currently underway to determine overall survival in the pre-chemotherapy setting
  - Side effects: fatigue, diarrhea, hot flashes, ***seizures*** (~1%)

CRPC MEDICATION SUMMARY

Medication	Mechanism	Overall Survival Hazard Ratio	Median Increase in Survival	Study
Pre-chemotherapy				
Sipuleucel-T	Active cellular immunotherapy	0.78	4.1 months	IMPACT**
Abiraterone	CYP17 inhibitor	0.79*	5.2 months*	COU-AA-302**
Enzalutamide (Experimental)	Androgen receptor modulator	Pending	Pending	PREVAIL **
Chemotherapy				
Docetaxel (Every 3 weeks)	Microtubule stabilization	0.62	2.4 months	TAX 327***
Cabazitaxel	Tubulin-binding	0.70	2.4 months	TROPIC***
Post-chemotherapy				
Abiraterone	CYP17 inhibitor	0.65	3.9 months	COU-AA-301**
Enzalutamide	Androgen receptor modulator	0.63	4.8 months	AFFIRM**
Radium-233	Bone metastasis targeted alpha radiation	0.70	3.6 months	ALSYMPCA**

** Trend was noted, but not statistically significant; statistically significant increase in median radiographic progression-free survival was 8.2 months.*

*** Medication vs. placebo trial*

**** Medication vs. Mitoxantrone trial*

| BONE METASTASIS TREATMENT |

- Reduce skeletal-related events (SRE) – may be pre- or post-castrate resistance
- Vitamin D (800-1,000 IU) and calcium (1,200 mg) supplementation daily
- Focal bone pain may be treated with XRT with good results
- Evaluate with bone scan and plain x-rays to rule out pathologic fractures
- **Zoledronic acid** (Zometa®): bisphosphonate
    - 4mg every 4 weeks
    - Must be renal dosed if GFR < 60
    - Side effects: musculoskeletal pain, flu-like symptoms, ***osteonecrosis of the jaw***
- **Denosumab** (Xgeva®): RANK Ligand inhibitor
    - 120mg every 4 weeks
    - No renal dose changes
    - Improved median time to SRE vs. zoledronic acid (20.7 vs. 17.1 months)
    - Side effects: ***osteonecrosis of the jaw***, hypocalcemia, fatigue, dyspnea
- **Strontium-89**: Radiopharmaceutical
    - Radioactive element selectively absorbed into bone, particularly osteoblastic lesions
    - Indication: treatment of ***osteoblastic bone lesion pain*** from metastatic prostate cancer
    - Half-life ~50 days (14 day washout in normal bone)
        - 25-65% pain improvement
- **Radium-233** (Alpharadin®): Alpha-pharmaceutical

  - ALSYMPCA trial showed an improved median overall survival in patients with CRPC and bone metastasis vs. placebo (14.9 vs. 11.3 months)
  - Half-life ~11 days

EPIDURAL CORD COMPRESSION

- Immediate MRI and intravenous Dexamethasone
  - 10mg loading dose, then 4-10mg every 6 hours; up to 100mg per day
  - Upon improvement, taper steroids over 2-3 weeks
- ***Radiation therapy***: usually definitive treatment
  - Surgical decompression prior may be better
- **Ketoconazole** (high dose)
  - 400mg every 8 hours, concomitant glucocorticoid
  - Inhibits 17-alpha-hydroxylase and 17,20-lyase (CYP17); effectively stopping adrenal and testicular androgen production
  - Castrate levels may be achieved in as little as 4 hours
  - Short term use only; as long term use loses testosterone suppression effect
- Bilateral orchiectomy is an option in ADT-naive patients

| HYPOGONADISM POST-PROSTATE CANCER TREATMENT |

- Testosterone replacement therapy may be considered in localized prostate cancer after treatment, an appropriate interval of time (at least 6 months) without recurrence, and a full understanding of the risk of recurrence
- May have a slight increase in PSA; however, maintain biochemical-recurrence reference values respective of the original treatment modality (e.g. Phoenix criteria for XRT)

| NEUROENDOCRINE TYPE PROSTATE CANCER |

- Histology: ***small cell carcinoma*** or ***poorly differentiated (anaplastic) carcinoma***
  - Paraneoplastic findings: somatostatin, chromogranin A, serotonin (increased urine metabolites), parathyroid hormone-related protein (subsequent hypercalcemia)

ADENOCARCINOMA VS. SMALL CELL / ANAPLASTIC SUBTYPE

Findings	Adenocarcinoma	Small Cell / Anaplastic
Metastasis	Bone, lymph nodes	Visceral (lung, liver), retroperitoneal soft tissue mass, and brain
Bone Lesions	Osteoblastic	Osteolytic
PSA	Elevated	Low / Undetectable
Chemotherapy	Docetaxel	Cisplatin and Etoposide

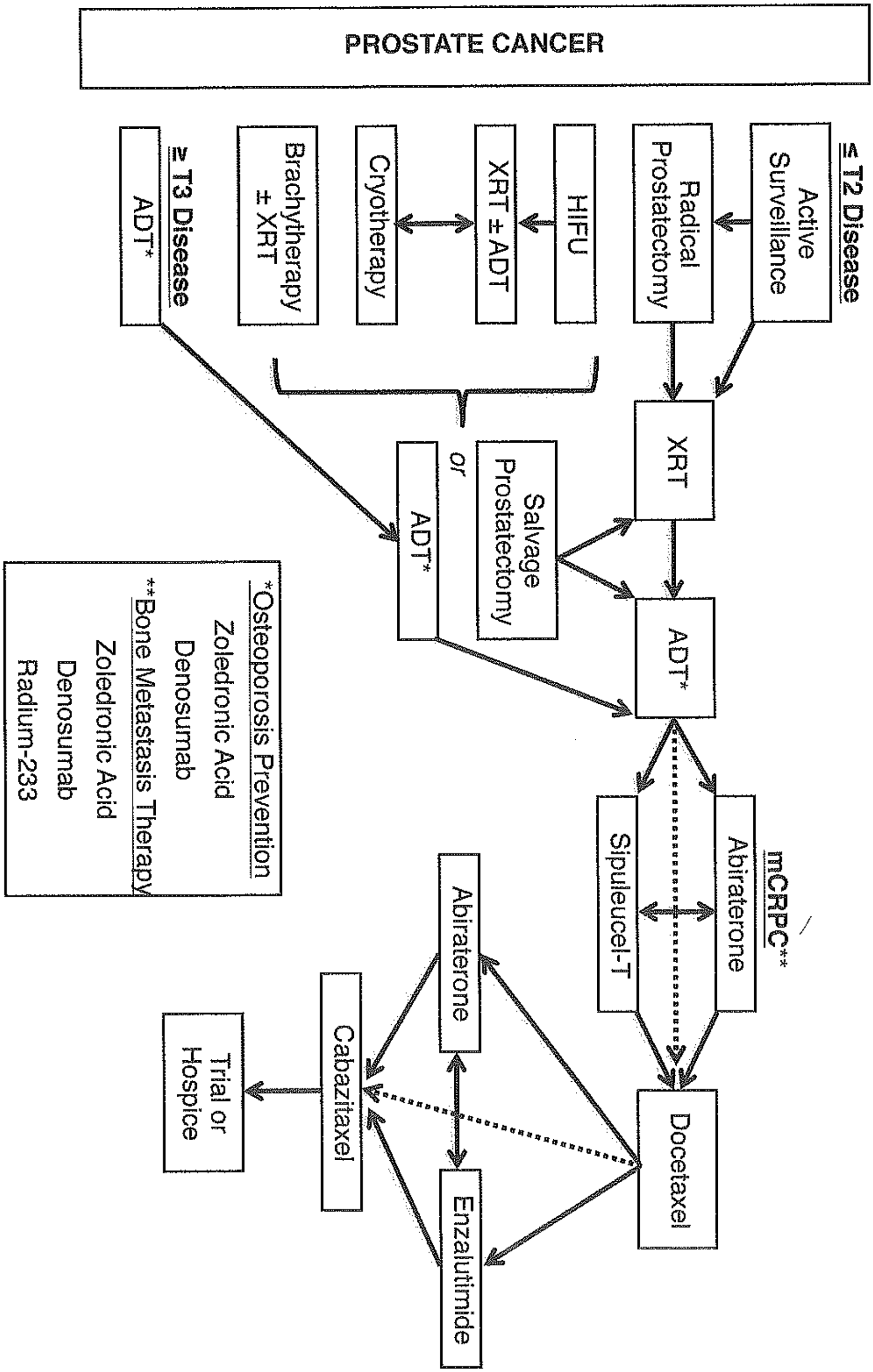
- Treatment options
  - ***Cisplatin and etoposide***
  - ***Highly Radiosensitive*** (may be in combination with chemotherapy)
  - Unresponsive to androgen deprivation therapy
- Poor prognosis

Small Cell / Anaplastic Prostate Cancer Treatment

Cisplatin and Etoposide

Radiation sensitive

PROSTATE CANCER ALGORITHM



CHAPTER 10: URETHRAL TUMORS

URETHRAL CARCINOMA

- Rare; usually presents in 40's
- Risks: ***HPV 16, 18 (SqCC)***, chronic inflammation/infection, urethral strictures, STD history
- Sx: bleeding, palpable mass, obstructing voiding symptoms, dysuria
- Dx: cystoscopy, urethral biopsy, penile MRI, CT scan for metastatic disease
- Urine cytology is not useful in this setting
- Staging Points: be sure to differentiate from bladder cancer extending into the prostate and primary urethral TCC
    - T2: Primary urethral TCC extends into the prostatic stroma or corpus spongiosum
    - T3: Extends into the corpus cavernosum, extracapsular extension, or bladder neck

MALE URETHRAL CARCINOMA

- Most common type: (1) ***SqCC*** (vast majority) (2) TCC (3) adenocarcinoma
- Most common location: (1) ***bulbomembranous*** (majority) (2) pendulous (3) prostatic
    - NOTE: Cowper glands enter at the bulbomembranous urethra and may contribute to a high incidence at this location

MALE URETHRAL CARCINOMA SUMMARY

	Posterior		Anterior*		
Urethral division	Prostatic	Membranous	Bulbous	Pendulous	Fossa navicularis
Epithelium	Transitional	Transitional	Pseudostratified columnar	Transition of pseudostratified columnar to stratified squamous	Stratified squamous
Lymphatic drainage	External iliac, internal iliac, obturator		Superficial & deep inguinal nodes, then external iliac **		
Treatment	Total penectomy with cystoprostatectomy and PLND if lacking distant metastasis		Partial penectomy with 2cm margin; if palpable nodes and no distant metastasis ILND		

** Better survival rates than posterior carcinomas*

*** Approximately 20% have palpable inguinal lymph nodes, and these are nearly always metastatic disease (remember penile carcinoma may have inflammatory lymph nodes)*

FEMALE URETHRAL CARCINOMA

- Most common type: (1) ***SqCC*** - 50% (2) TCC – 20% (3) adenocarcinoma – 10-20%
    - o Adenocarcinoma may arise from Skene's glands and produce PSA
    - o Adenocarcinoma is more common to result in distant metastasis
- Palpable lymph nodes are almost always a result of metastatic disease
- Rarely, squamous cell carcinoma may arise from a urethral diverticulum
- Sx: bleeding or palpable urethral mass

FEMALE URETHRAL CARCINOMA SUMMARY

	Proximal (“Posterior”)	**Distal (“Anterior”) ***
Urethral division	Proximal 2/3	Distal 1/3
Epithelium	Proximal 1/3: Transitional Mid 1/3: Stratified squamous	Stratified squamous
Lymphatic drainage	External iliac, internal iliac, obturator (20% at presentation)	Superficial & deep inguinal nodes, then external iliac (25% at presentation)
Treatment	Anterior pelvic exenteration with PLND without distant metastasis; consider chemo / radiation	Distal urethrectomy with ILND if palpable nodes without distant metastasis

* *Distal female urethra may be excised without causing incontinence*

CHAPTER 11: PENILE TUMORS

| BENIGN LESIONS |

CONDYLOMA ACUMINATA

- Genital warts
- ***HPV 6, 11***
- Histology: ***Koilocytes*** (appears as "Owl's eye"), hyperkeratosis
- Dx: acetowhite lesions = 5% acetic acid (vinegar) identifies hyperkeratosis associated with HPV
- Prophylaxis: Quadrivalent HPV recombinant vaccine for HPV 6, 11, 16, 18
    - Male and females aged 9-26 years old
- Tx: Podophyllum resin, Podofilox, Imiquimod 5%, cryotherapy, CO2 laser, excision

BUSCHKE-LOWENSTEIN TUMOR (GIANT CONDYLOMA ACUMINATA)

- Aka Verrucous Carcinoma
- Verrucous, destructive, slow growing tumor that is induced by ***HPV***
- Usually does not metastasize, but may be quite invasive and destructive
- Tx: wide surgical excision followed by topical condyloma acuminata treatments; cryotherapy

PEARLY PENILE PAPULES

- ***Non-contagious***, small, white papules that circumferentially line the corona of the glans penis
- Relative common, and mistaken as genital warts; not associated with HPV
- Tx: reassurance
    - If for cosmesis: CO2 laser, electrocautery, or excision

ANGIOKERATOMA OF FORDYCE

- Hyperkeratotic veins located on the scrotum, penis, labia majora that appear as blue-purple spots
- Tx: reassurance
    - If for cosmesis: CO2 laser, electrocautery, or excision

FORDYCE'S SPOTS

- Ectopic sebaceous glands not associate with hair follicles
- Appear as yellow / white, painless papules that appear on the genitals
- Tx: reassurance
    - If for cosmesis: CO2 laser, electrocautery, or excision

FIXED DRUG ERUPTION

- Tetracycline, sulfonamides, NSAIDS, and aspirin are common etiologies
- Often confused with other conditions
- Sx: red macules, blistering, erosions, ulcerations
    - Will recur at the same site with each subsequent exposure to the offending agent
- Tx: stopping the offending agent will resolve the eruption

ZOON'S BALANITIS

- Aka: Balanitis circumscripta plasmacellularis
- Chronic inflammatory disease of penile glans and prepuce
- Histology: ***plasma cells***

- DDx: Erythroplasia of Queyrat, BXO
- Tx: topical steroids; topical tacrolimus (calcineurin inhibitor); circumcision; CO2 laser ablation

| PREMALIGNANT LESIONS |

- Strong association between penile premalignant lesions and inflammation
- Smegma is not considered a carcinogen
- All conditions require annual follow up to evaluate for progression

BOWENOID PAPULOSIS

- Maculopapular lesions on penile shaft; induced by ***HPV 16, 18***; found most commonly in young men
- ***Majority run benign course***; however, known to have transformation to SqCC
- Histology: similar carcinoma in situ
- Some consider this a transition point between genital warts and Bowen's disease (often confused with Bowen's disease)
- Tx: lesion destruction (excision, electrocautery, cryotherapy, CO2 laser, topical 5-fluorouracil (5-FU))

LEUKOPLAKIA

- White plaques usually on glans or prepuce and are associated with ***SqCC***
- If ulceration, erosion, or fissures: suspect malignancy
- Tx: surgical excision, circumcision

LICHEN SCLEROSUS ET ATROPHICUS (BALANITIS XEROTICA OBLITERANS – BXO)

- Chronic, progressive, atrophic, whitish and indurated skin of the glans and prepuce; may cause meatal stricture
- Etiology is unclear; may be autoimmune

- Dx: biopsy – associated with SqCC
  - Biopsy if atypical appearance, rapidly worsening or poor response to treatment
- Tx: topical steroid (e.g. betamethasone, lotrisone), circumcision, meatotomy/urethroplasty, topical Tacrolimus
  - If asymptomatic, may offer observation

PENILE HORN

- Cutaneous horn on the glans associated with HPV 16
- SqCC (up to 30%)
- Tx: excision

HPV Types

Low Risk for Neoplasia: 6, 11

High Risk of Neoplasia: 16, 18, 31, 33, 35, 39, 45

| PENILE CARCINOMA |

PENILE CARCINOMA

- Rare cancer in the USA
- Most common in men 50-70 years old
- **Risk factors:** phimosis, uncircumcised, smoking, Human Papilloma Virus (HPV)/genital warts, chronic inflammation
  - Neonatal circumcision nearly eliminates risk for penile cancer
  - Prepubertal circumcision may decrease penile cancer risk
  - Postpubertal circumcision does not change risk
- Vast majority of penile cancer is squamous cell carcinoma (SqCC)
- Most common associated paraneoplastic syndrome is hypercalcemia
- Mainstay of penile cancer treatment is tumor resection (e.g.

penectomy), except some superficial lesions may be destroyed (e.g. laser, cryotherapy)

  - May biopsy prior definitive surgery

- Staging Points:
  - T1a: low grade subepithelial connective tissue invasion
  - T1b: is T1a with lymphovascular invasion (LVI) or high grade ± LVI
  - T2: any of the corporeal bodies
  - T3: urethral invasion
  - For further staging details: http://www.cancer.net/cancer-types/penile-cancer/staging-and-grading

SQUAMOUS CELL CARCINOMA IN SITU

- **Bowen's Disease**
  - SqCC in situ located on the ***penile shaft***
- **Erythroplasia of Queyrat**
  - SqCC in situ located on the ***glans penis or prepuce***
    - * Nearly exclusive seen in uncircumcised men
- Usually well-marginated, and appears as erythematous plaques
- Associated with HPV 16, 18 and may progress to invasive SqCC
- Dx: biopsy
- Tx: surgical excision, Mohs micrographic surgery, circumcision, CO2 laser, 5-FU topical or 5% Imiquimod cream

Squamous Cell Carcinoma In Situ

Bowen's disease: penile shaft

Erythroplasia of Queyrat: glans penis or prepuce

INVASIVE SQUAMOUS CELL CARCINOMA

- Associated with ***HPV 16, 18, 31, 33***
- Location (approximate): Glans 50%, Shaft 30%, Prepuce (20%)
- Sx: non-healing penile lesion, papule, wart, induration, ulcerations, fungating lesion
- Dx: biopsy
  - If positive lymph nodes or high stage/grade: chest x-ray, CT scan abdomen/pelvis, serum calcium, liver function panel
  - Bone scan if elevated calcium, pathologic fracture, elevated alkaline phosphatase
- Tx: excision (circumcision vs. partial vs. total penectomy) with ***frozen section for negative margins***; Mohs micrographic surgery (small, superficial invasive carcinoma and CIS); penile glans excision with outer preputial flap or split thickness skin graft; radiation (external beam / brachytherapy); laser; chemotherapy
  - If conservative treatment, follow up for at least 10 years

PENECTOMY

- Many partial penectomies retain sexual function
- Must have ***at least 2 cm*** stump for voiding function, otherwise will need perineal urethrostomy
- Classically, partial penectomies needed a 2cm margin; however, ***negative surgical margins*** is key, thus allowing further penile preservation
- Total penectomy is indicated for T2 disease and Grade 3 disease (***invasion into the corpora cavernosum***)
  - If total penectomy, will need perineal urethrostomy
- ***Lymphovascular invasion*** – highly predictive of inguinal lymph node metastasis
- ***Metastatic penile cancer*** is treated with systemic chemotherapy vs. radiation vs. chemo/radiation; then possible penectomy
  - Most common sites: lung > liver > bone
- ***Chemotherapy = paclitaxel, ifosfamide, cisplatin (TIP)*** indications
  - Pelvic lymph nodes
  - Bilateral inguinal lymph nodes

  - Lymph node > 4cm
  - Distant metastasis

INGUINAL LYMPHADENECTOMY

- Lymph node involvement has the greatest impact on prognosis
- ***Antibiotic*** for six week course is no longer recommended, rather fine needle aspiration is preferred
- Sentinel lymph node biopsy is controversial and generally not recommended
- Typical lymph node spread pattern: superficial inguinal → deep inguinal → pelvic → distant metastasis
- If ***non-palpable inguinal lymph nodes***
  - ≤ T1a: may observe
  - ≥ T1b: bilateral superficial modified inguinal lymph node dissection (ILND), and if positive nodes, proceed on that side(s) with classic ILND for superficial and deep nodes
- If ***palpable inguinal lymph nodes***
  - ≤ 4cm: fine needle aspiration
    - Negative = excisional biopsy (if positive = ILND)
    - Positive = ILND
  - ≥ 4cm: ILND vs. chemotherapy vs. radiation
- If ***unilateral inguinal lymph nodes***, will need ipsilateral superficial and deep ILND and contralateral superficial ILND. If the contralateral superficial nodes are positive, then deep ILND as well.
  - ***Superficial***: nodes ***anterior to the fascia lata***
    - Nodes run along inguinal ligament and down great saphenous vein
  - ***Deep***: nodes ***posterior to the fascia lata***; medial to the femoral vein
    - 3-4 nodes in this area and track back to external iliac nodes
    - ***Node of Cloquet*** = most superior node of inguinal lymph nodes (also, most distal external iliac lymph node); lies within the femoral canal

  - Approximately 1/3 of inguinal lymph node clinical metastasis are found to be pathologically negative after ILND
- If ***pelvic lymph nodes***: neoadjuvant chemotherapy vs. chemo/radiation, then surgical excision in responders
  - Approximately 25% of all patients with metastatic inguinal lymph nodes will have positive pelvic nodes

RADICAL INGUINAL LYMPH NODE DISSECTION

- ***Classic radical ILND***
  - Superior = inguinal ligament, medial = adductor longus, lateral = sartorius (open ***fascia lata*** to access deep nodes)
  - Resect Saphenous vein; Sartorius transposition
- ***Modified radical ILND***
  - Excludes dissection of the area lateral to femoral artery (i.e. femoral nerve area) and distal to fossa ovalis (i.e. saphenous opening; preserves the great saphenous vein); also exclude sartorius transposition
  - Decreased morbidity
- **Complications:** up to 50%; lymphedema, wound infection, dehiscence, lymphocele, flap necrosis, seroma, thrombosis

SUMMARY OF INGUINAL LYMPH NODE DISSECTION TEMPLATES

ILND	Superior	Medial	Lateral	Saphenous	Sartorius
Classic	Inguinal ligament	Adductor longus	Sartorius	Resection	Transposition
Modified	Inguinal ligament	Adductor longus	Femoral artery	Preservation	No transposition

METASTATIC TUMOR TO THE PENIS

- Most common primary tumors: bladder, prostate, colorectal
- May present as ***priapism***
- Sign of advance primary tumor disease; poor prognosis

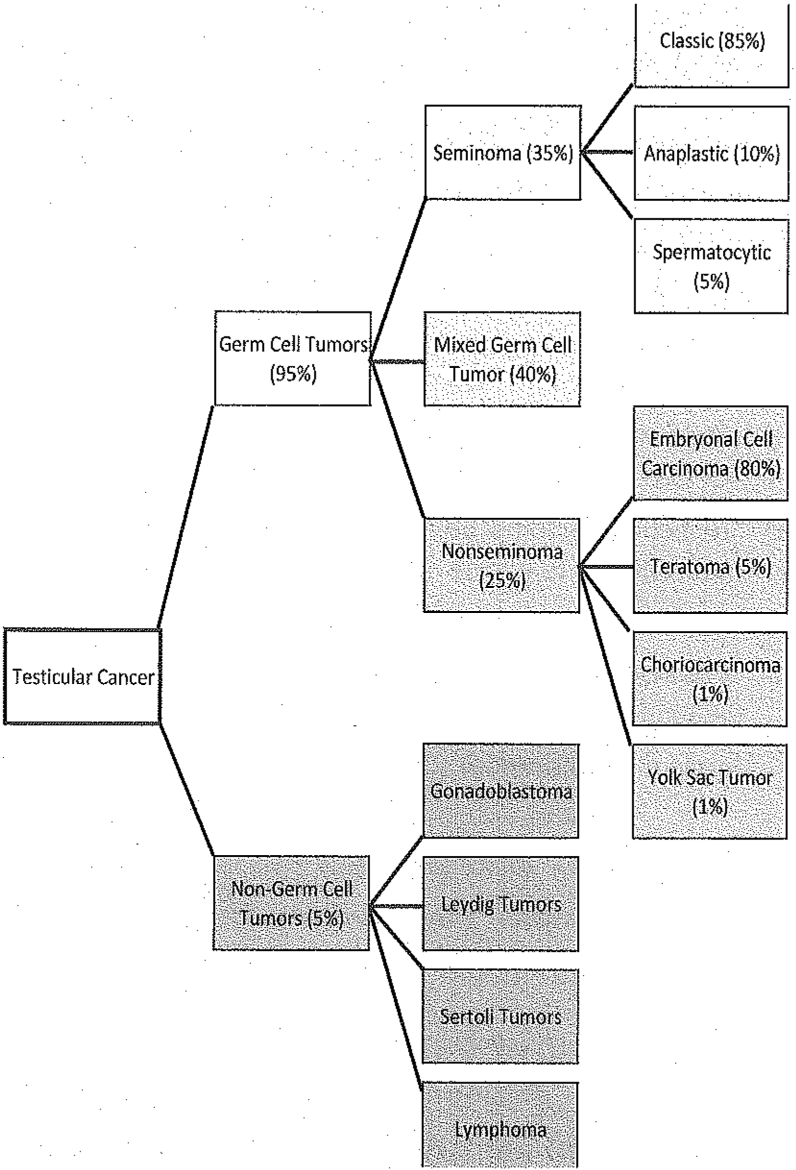
PENILE MELANOMA

- Very rare
- ABCD's of melanoma
  - o **A**symmetry
  - o **B**order irregularity
  - o **C**olored variability
  - o **D**iameter > 6 mm
- Dx: biopsy
- Tx: excision (e.g. circumcision, partial or total penectomy); inguinal lymph node metastasis is common

KAPOSI SARCOMA

- Very rare; reticuloendothelial system tumor
- AIDS patients and immunosuppressed
- Tumor of ***Herpes virus 8***
- Bluish papule or ulceration
- Tx: optimize HIV/AIDS therapy (HAART); radiation

CHAPTER 12: TESTICULAR TUMORS



| RISK FACTORS |

- Most common age for testicular cancer (CaT) is 20-40 years old
    - ***Pediatrics: yolk sac and teratoma***
    - ***20-30 years old: non-seminoma***
    - ***35-40 years old: seminoma***
    - ***> 50 years old: lymphoma and spermatocytic seminoma***
- Incidence = 1:300 (white > black)
- ~ 95% of CaT is Germ Cell Tumors (GCTs)
- **Risk factors**: cryptorchidism, gonadal dysgenesis, family history, androgen insensitivity syndrome
- **Cryptorchidism**: up to 4% of kids at birth; however, only 1% by 1 year of age
    - Relative risk (RR) overall for CaT = 3-8X
    - RR for CaT if prepubertal orchidopexy = 2-3X
    - RR for CaT if postpubertal orchidopexy = 2-6X > prepubertal orchidopexy
    - Contralateral, normal descended testicle is not at increase RR for CaT
    - Testicular nubbins have virtually zero risk of malignancy, and not required to excise
    - ***Pre-orchidopexy*** = higher RR for ***seminoma (~75%)***
    - ***Post-orchidopexy*** = higher RR for ***non-seminoma (~66%)***
    - Tx: orchidopexy is preferred at 6 months of age (1 year was previous preference)

CRYPTORCHIDISM TREATMENT BASED ON AGE AND HEALTH STATUS

Age	Overall Health (ASA score)	Treatment
< 10-12 (Prepubertal)	---	Orchidopexy
12 - 50	ASA 1 or 2	Orchiectomy
12 – 50	ASA 3 or 4	Observation
> 50	---	Observation

- **Intratesticular microlithiasis** is associated with testicular cancer; however, it is not considered a risk factor
    - o If history of CaT, then increased risk of testicular CIS
- Sx: hydrocele, gynecomastia, precocious puberty, back pain, scrotal swelling; testicle may be painful or painless

| TUMOR MARKERS |

ALPHA-FETOPROTEIN (AFP)

- Glycoprotein secreted by fetal yolk sac, liver and intestine
- Half life = ***5-7 days*** (Mnemonic: alpha has 5 letters, t½ is 5 days)
- Normally < 10 ng/mL
- If liver damage (e.g. alcoholism, hepatitis), AFP may remain elevated
- ***AFP is never elevated in pure choriocarcinoma and pure seminoma***

BETA-HUMAN CHORIONIC GONADOTROPIN (B-HCG)

- Protein secreted by ***syncytiotrophoblasts***
- Alpha subunit: homologous with LH, FSH, TSH

- Beta subunit: ~ 70% homologous with LH; however, unique c-terminal amino acid sequence
  - Hypergonadotropic hypogonadism (low testosterone, high LH) may create falsely elevated β-hCG due cross-reactivity
    - Administer testosterone 200mg IM (decreases LH) and re-check β-hCG in 48 hours
- Half life = ***24-36 hours***
- Normally < 5 mIU/mL
- ***β-hCG may be elevated in embryonal, choriocarcinoma, and ~ 20% of classic seminoma***

LACTATE DEHYDROGENASE (LDH)

- Enzyme secreted by many organs
- ***Marker of bulky disease***

PLACENTAL ALKALINE PHOSPHATASE (PLAP)

- Marker of advanced disease
- Rarely used in clinical setting

SUMMARY OF TESTICULAR CANCER TUMOR MARKERS

Testicular Cancer	AFP	β-hCG
Seminoma		
- Classic	---	20%*
- High mitotic index	---	---
- Spermatocytic	---	---
Embryonal Carcinoma	+	+
Teratoma	+	---
Yolk Sac Tumor	**~ 100%**	---
Choriocarcinoma	---	**100%**

** Classic seminoma is only mildly elevated, usually 100-200 mIU/mL*

- NOTE: ~ 10% of patients post-chemo with normal markers will still have CaT
- Common for marker surge 2-3 weeks after starting chemotherapy, then proportional to amount of tumor
- Post-orchiectomy tumor marker normalization takes ~ 5 half-lives. Note that normalization does not guarantee cure.

| IMAGING |

- Must rule out metastatic disease
- **Scrotal ultrasound**: diagnostic for testicular cancer
- **Abdominal CT scan**: prior radical orchiectomy for retroperitoneal staging
- **Chest X-ray** (CXR): prior radical orchiectomy for staging
    - If an abnormal CXR or abdominal CT scan → ***chest CT scan***
- **MRI scan**: useful for evaluation of vessel involvement prior retroperitoneal lymph node dissection
- **PET scan**: becoming more useful; especially in seminoma

| CARCINOMA IN SITU (CIS) |

INTRATUBULAR GERM CELL NEOPLASIA = CIS

- Precursor for all germ cell tumors, except spermatocytic seminoma, yolk sac tumors and mature teratomas
- Almost always found adjacent to CaT
- If CIS is not treated, 50% will progress to CaT within 5 years!
- Tx: radical orchiectomy, radiation, chemotherapy, observation

| SEMINOMA - GERM CELL TUMORS |

SEMINOMA

- Origin: spermatocyte
- Sensitive to ***chemotherapy*** and ***radiation***
- **Classic seminoma** – 85%
    - Men > 35 years old
    - ~ 20% have syncytiotrophoblasts with ***mild β-hCG elevation***
    - Histology: ***fried egg appearance***; large uniform cells; clear cytoplasm; well defined cell borders
    - Most likely CaT to have ***bone*** metastasis
    - Homologous in female as dysgerminoma in the ovary
- **Seminoma with high mitotic index (anaplastic)** – 5-10%
    - ≥ 3 mitoses/hpf
    - Prognosis same as classic seminoma
    - Also associated with ***mild β-hCG elevation***
- **Spermatocytic** – (< 5%)
    - Men > 50 years old
    - DDx: lymphoma
    - Histology: variation in size (small, medium, large); non-clear cytoplasm
    - No tumor marker elevation
    - No metastatic potential; local disease only
    - Tx: radical orchiectomy; no chemo necessary
- ***Seminomas mixed with non-seminoma tumors are treated as non-seminoma!!!***

| NON-SEMINOMA - GERM CELL TUMORS |

EMBRYONAL CARCINOMA

- Origin: Blastocoel (early embryo)
- Usually men 20-30 years old
- Histology: usually mixed (rarely pure), vascular and tunica invasion common
- May have elevated ***AFP or β-hCG***
- Prognosis: worst of all germ cell tumors

YOLK SAC TUMOR

- Origin: embryo yolk sac
- Bimodal distribution: 1-2 years old (pure) and 25-25 years old (mixed)
- Histology: ***Schiller-Duval bodies***
- Nearly 100% have elevated ***AFP***
- ***Most common pediatric testicular carcinoma***

CHORIOCARCINOMA

- Origin: chorionic villus
- Pure is exceedingly rare; usually mixed
- ***All have elevated β-hCG***
- Only tumor with hematogenous metastasis; all others are lymphatic based
    - ***High rate of brain metastasis***
- Worst prognosis of all testicular tumors (most lethal; however, it's the least common, ~1%)

TERATOMA

- Origin: embryo (endoderm, ectoderm, and mesoderm elements)
- Bimodal distribution: < 4 years old and 20-40 years old
- ***Mature teratoma = benign***
    - Nearly all are prepubertal teratomas!

  - May enucleate
- ***Immature teratoma = malignant***
  - Poorer prognosis
- Tx: surgical excision; ***chemo and radiation resistant***

| STAGING |

- Staging Points: staging is post-orchiectomy
  - T1: extends into tunica albuginea without lymphovascular invasion (LVI)
  - T2: extends into tunica albuginea + LVI, or extends into tunica vaginalis ± LVI
  - T3: spermatic cord invasion
  - T4: scrotum invasion
  - For further staging details: http://www.cancer.net/cancer-types/testicular-cancer/staging

STAGING SUMMARY

- **Stage 0**: testicular CIS
- **Stage 1**: no evidence of metastatic disease
- **Stage 2**: retroperitoneal metastasis
- **Stage 3**: distant metastasis
  - ***Pulmonary metastasis***: good prognosis
  - ***Visceral metastasis***: poor prognosis

TESTICULAR TUMOR MARKER RISK CATEGORIES

Markers	Good (S1)	Intermediate (S2)	Poor (S3)
AFP (ng/mL	< 1,000	1,000 – 10,000	> 10,000
β-hCG (mIU/mL)	< 5,000	5,000 – 50,000	> 50,000
LDH	< 1.5X ULN	1.5-10X ULN	> 10X UNL

** UNL = upper limit of normal*

HINT: only memorize the intermediate values, and extrapolate the others.

TESTICULAR CANCER RISK CATEGORIES

Risk	Seminoma	Nonseminoma
Good	Stages 1, 2, and 3 with pulmonary metastasis only (no other visceral metastasis)	Good markers +/- pulmonary metastasis
Intermediate	Stage 3 with non-pulmonary visceral metastasis	Intermediate markers +/- pulmonary metastasis
Poor	None	Mediastinal primary, non-pulmonary visceral metastasis, or poor markers

PET SCAN STATISTICS (APPROXIMATE)

Germ Cell Tumor	Sensitivity	Specificity	PPV	NPV
Seminoma *	80%	~100%	100%	95%
Nonseminoma	70%	50%	60%	50%

** PET scan in pure seminoma with residual mass > 3 cm on CT scan*

- The above table illustrates why ***PET scan is only useful for seminoma***

| TREATMENT |

RADICAL ORCHIECTOMY

- ***Inguinal incision*** is the initial gold standard for CaT
    - If large tumor and difficult to extract from scrotum, extend incision into upper scrotum. It is more important to avoid tumor spillage than incising the superior scrotum
- In advanced disease, neoadjuvant chemotherapy may be done to avoid treatment delay
- ***If seminoma with contralateral CIS, treatment is orchiectomy for seminoma and XRT for contralateral CIS.***
- **Scrotal violations:** subsequent treatment is controversial
    - Stage 1 disease: equivalent survival rates, but affects ***local recurrence*** rates:
        - * ~ 0.5% high inguinal incisions
        - * ~ 3% scrotal violations
    - Previously, inguinal and hemiscrotal radiation and/or hemiscrotectomy were performed; however, these are morbid interventions, but they do decrease recurrence
    - Currently, scar resection may be considered at time of RPLND for NSGCT, and if low stage seminoma, consider groin XRT.

PARTIAL ORCHIECTOMY

- Indications – only for non-hypogonadal men (will still be infertile from XRT)
    - Bilateral CaT
    - Solitary testicle with CaT
    - Tumor < 2cm or < 30% of testicular volume
    - Polar location
- ***Adjuvant external beam radiation (20Gy) if CIS is present*** (biopsy remaining ipsilateral testicular tissue at time of orchiectomy)

CHEMOTHERAPY

- **Bleomycin**
    - Produces free radicals and breaks DNA strands
    - SE: pneumonitis, pulmonary fibrosis (~1%)
    - Minimize intraoperative fluids to reduce risk of postoperative respiratory failure
- **Etoposide (VP-16)**
    - Inhibits DNA topoisomerase II → breaks DNA strands
    - SE: myelosuppression (~80-90%), gastrointestinal upset
- **Cisplatin**
    - Forms intrastrand DNA crosslink adducts
    - SE: nephrotoxicity (~33%), ototoxicity (~33%), myelosuppression (~25%), secondary malignancy (e.g. leukemia)
- BEP increases the risk of cardiovascular disease by ~ 1.5 fold; while mediastinal XRT increases the risk of myocardial infarction by ~ 4 fold
- **2nd Line Chemotherapy**
    - ***VeIP*** = Vinblastine, Ifosfamide, Cisplatin
    - ***TIP*** = Paclitaxel, Ifosfamide, Cisplatin

EXTERNAL BEAM RADIATION THERAPY (XRT)

- Only indicated for ***seminoma***
- Side effects: secondary malignancy, coronary vascular disease (pulmonary field XRT), hypogonadism and infertility (most testicular cancer patients are sub-fertile at time of diagnosis)
    - ***Leydig cells and spermatogonia are radiation sensitive!***
    - All patients interested in childbearing should consider sperm banking

RETROPERITONEAL LYMPH NODE DISSECTION (RPLND)

- **Left CaT**: para-aortic and inter-aortocaval nodes
- **Right CaT**: inter-aortocaval and paracaval nodes
    - ***Right CaT nodes have high crossover rate to the left sided nodes***

Testicular Cancer Lymph Node Crossover Mnemonic

Lymphatics in abdomen flow right to left via cisterna chyli to the thoracic duct, which drains in to the left subclavian vein

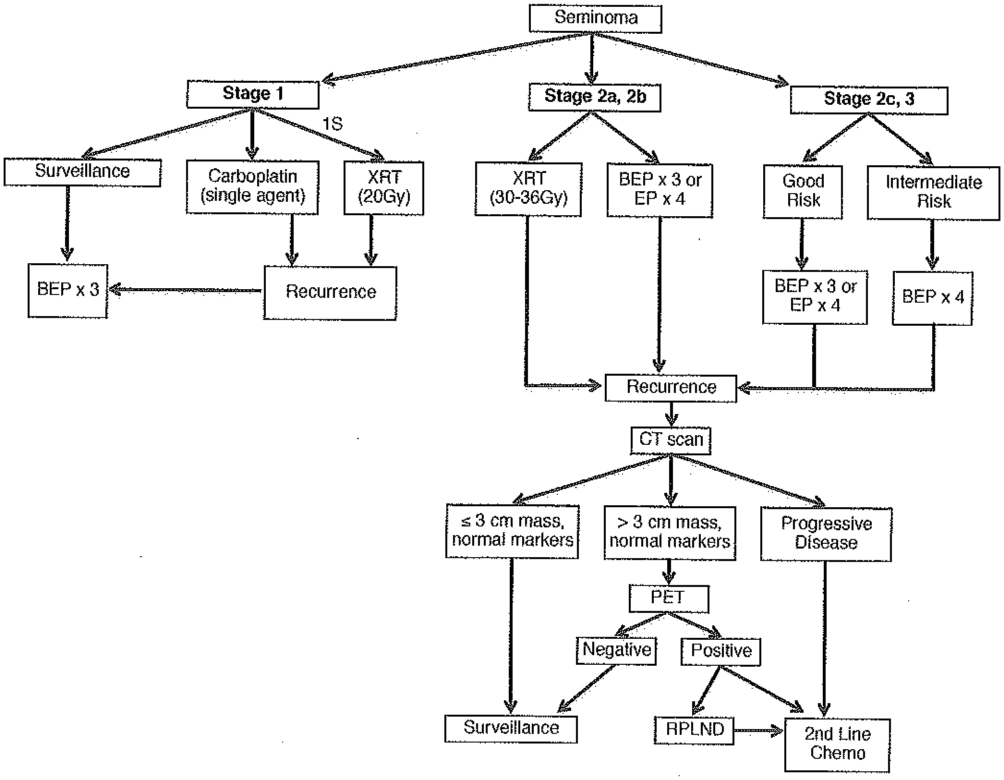
- All GCT's, except choriocarcinoma (hematogenous), metastasize via lymphatics
- Majority of metastatic adenopathy is to the retroperitoneum; however, if spermatic cord invasion, metastasis may include the pelvic and/or inguinal lymph nodes
- Complications – Primary RPLND: overall ~ 10%
  - Wound infection (most common); atelectasis; small bowel obstruction
- Complications – Post-Chemo RPLND: overall 20-35%; ~ 1% mortality rate
  - Pulmonary complication (most common) – related to Bleomycin interstitial fibrosis; wound infection; small bowl obstruction; chylous ascites; lymphocele
- ***Nerve sparing RPLND***: the sympathetic (emission) and pudendal (ejaculation) nerves and plexuses are preserved
  - Preserve the postganglionic sympathetic chains run anterior to the aorta and surround the origin of the inferior mesenteric artery
  - > 95% maintain emission and antegrade ejaculation
- Resect persistent pulmonary NSGCT metastasis after RPLND

RPLND TEMPLATES

	Right-Modified	Left-Modified	Post-chemo
Superior	Renal veins	Renal veins	Renal veins
Medial *	Left edge of aorta	Left edge of IVC	Contralateral ureter
Lateral	Right ureter	Left ureter	Ipsilateral ureter
Inferior	IMA (spared)	IMA (spared)	Common iliacs
Distal	Right iliac artery to ureteric crossing	Left iliac artery to ureteric crossing	Bilateral iliac artery to ureteric crossing

** Extend the medial margin to the contralateral ureter for the bilateral-modified*

SEMINOMA TREATMENT ALGORITHM*

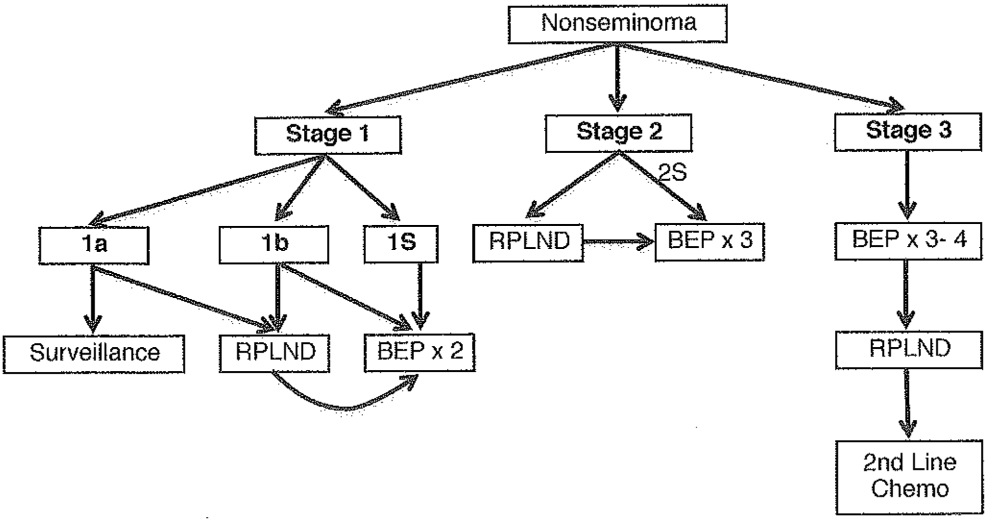


BEP = Bleomycin, Etoposide (VP-16), Cisplatin; XRT = External beam radiation therapy; 2nd Line Chemo = VeIP (Vinblastine, Ifosfamide, Cisplatin) or TIP

(Paclitaxel, Ifosfamide, Cisplatin)

** Note: If bulky lymphadenopathy (≥ 5 cm; Stage 2c), the next step is chemotherapy, and radiation is no longer an option!*

NONSEMINOMA TREATMENT ALGORITHM*



BEP = Bleomycin, Etoposide (VP-16), Cisplatin; RPLND = retroperitoneal lymph node dissection; 2nd Line Chemo = VeIP (Vinblastine, Ifosfamide, Cisplatin) or TIP (Paclitaxel, Ifosfamide, Cisplatin)

** Note: If elevated markers (i.e. 1S or 2S) proceed directly to chemotherapy!*

NONSEMINOMA, POST-CHEMOTHERAPY, RETROPERITONEAL MASS

- **Fibrosis / necrosis**
  - CT scan without any lymph nodes > 8mm is highly predictive of fibrosis
- **Teratoma** (Growing Teratoma Syndrome)
- **Residual nonseminoma**
- **Malignant transformation of teratoma** (e.g. sarcoma, adenocarcinoma)
- **Post-chemotherapy treatment = controversial, if marker normalization**

  - No residual mass + marker normalization = ***observation***
  - Residual mass + marker normalization = ***RPLND / mass excision***
  - Persistent marker elevation = ***salvage chemotherapy (2nd line)***
  - Some authorities recommend post-chemo RPLND for all patients with marker normalization

FOLLOWUP

- Poor prognostic features for recurrence: (1) ***lymphovascular invasion*** – most important for occult metastasis, (2) rete testes invasion (particularly seminoma), (3) large tumor size > 4cm, (4) aggressive tumor histology
- **Testicular exam**: monitor remaining testicle for tumor routinely; ~ 2% risk over the next 15 years
- **Tumor markers**: variable depending on stage (every 2-4 months, then semi-annual, then annually); nonseminoma is more rigorous, and add chest x-ray with markers
- **Abdominal CT scan**: variable depending on stage (every 6-12 months for 1-3 years, then annually); nonseminoma is more rigorous depending on treatment modality
- Lung is the most common site for NSGCT recurrence after RPLND

| NON-GERM CELL TUMORS |

- ~ 5% of all testicular tumors
- Majority are benign
  - Malignant features: > 5 cm, high mitotic activity, lymphovascular invasion, paratesticular structure invasion

ADENOMATOID TUMOR

- ***Benign***, extratesticular tumor of the mesothelium
- ***Most common benign extratesticular tumor***
- Most commonly found on the epididymis

LEYDIG (INTERSTITIAL) CELL TUMORS

- Rare (~ 3% of testicular tumors)
- Histology: Reinke's crystals – rod-like
- ~ 33% have symptoms related to testosterone / estrogen
    - Gynecomastia, precocious puberty
- Lab: ***elevated urinary 17-ketosteroids*** (i.e. androgen breakdown products, such as DHEA and androsterone)
    - DDx: 21-hydroxylase congenital adrenal hyperplasia (***elevated urinary pregnanetriol and urinary 17-ketosteroids***)
- Tx: orchiectomy or mass enucleation
    - Chemotherapy / radiation resistant
    - Possible role for RPLND

SERTOLI CELL TUMORS

- Rare (< 1% testicular tumors)
- Histology: Charcot-Bottcher filaments
- ~ 33% have symptoms related to testosterone / estrogen (e.g. gynecomastia, without virilization)
- Sclerosing (no hormonal symptoms) and large-cell calcifying variants (associated with Carney or Peutz-Jeghers Syndrome)
- Tx: orchiectomy
    - Chemotherapy / radiation resistant
    - Possible role for RPLND

GONADOBLASTOMA

- Very rare; usually benign
- May transform into malignant germinoma (i.e. seminoma)
- Exclusive to patients with ***disorders of sexual development (intersex)***
    - Turner's Syndrome and 45,XO/46,XY mosaic
- Tx: orchiectomy if Y chromosome present on the karyotype

LYMPHOMA

- Usually in men > 50 years old
- ***Non-Hodgkin's*** type only
- Most common testicular tumor in men > 50 (2nd most common is spermatocytic seminoma); and most common metastatic tumor to the testis
- Often presents bilaterally
- Ultrasound: multiple hypoechoic lesions
- Tx: ***orchiectomy with chemotherapy +/- radiation***

LEUKEMIA

- Usually young boys; many are bilateral
- Acute lymphocytic leukemia
- Tx: ***chemotherapy***

METASTATIC TUMORS

- Prostate
- Lung
- Melanoma
- Renal cell carcinoma

LIPOSARCOMA / LEIOMYOSARCOMA OF PARATESTICULAR STRUCTURES

- Rare, usually well differentiated
- Low grade = ***high inguinal orchiectomy***
- High grade = ***high inguinal orchiectomy +/- radiation***

TESTICULAR ADRENAL REST TUMORS (TART)

- Found in ***21-hydroxylase deficiency***
- Usually present with bilateral testicular masses
- Tx: ***glucocorticoids*** result in tumor regression
  - o Do not perform orchiectomy for TART

SUBTUNICAL TESTICULAR CYSTS

- Routine ultrasound monitoring if complex cyst to rule out malignancy

CHAPTER 13: PRIMARY RETROPERITONEAL TUMORS

- ***Retroperitoneum***: posterior compartment defined anteriorly by parietal peritoneum and posteriorly by transversalis fascia
- < 0.2% of all malignancies
- ~ 70% of retroperitoneal tumors are malignant lesions
- Sx: abdominal mass / pain / distention, low back pain
- Tx: surgical excision is primary treatment; XRT may have a role

LIPOSARCOMA

- Origin: mesenchyme
- Most common in 40-60 year olds; female = male
- Histology: well-differentiated, myxoid (50%), pleomorphic, and round cell variants
  - Usually large tumors (e.g. > 20 cm)
  - Calcification may help differentiate from other tumors
- Dx: CT scan: ***negative Hounsfield units*** because adipose tissue
  - MRI T1 – high signal intensity; T2 – intermediate signal intensity
- Tx: surgical resection with 1-2 cm surgical margin
  - Local progression is common (complete resection is difficult)
  - Chemotherapy is experimental

LEIOMYOSARCOMA

- Origin: smooth muscle, blood vessels or Wolffian duct remnants
- Most common in 40-50 year olds; female > male

- Also large tumor (e.g. > 10 cm)
- Dx: CT: ***necrosis / hemorrhage and vessel involvement are common***
    - MRI T1 – low signal intensity; T2 – high signal intensity
- Tx: surgical resection
    - Common recurrence (complete resection is difficult)

RHABDOMYOSARCOMA

- Most commonly seen in pediatrics
- See Pediatric Tumors Chapter

OTHER MALIGNANCIES

- Fibrous histiocytoma, mesenchymoma, lymphoma, hemangioendothelioma, neurofibroma, Paraganglioma, schwannoma, teratoma, undifferentiated sarcomas

| RETROPERITONEAL FIBROSIS |

- Most commonly seen in 40-60 years old
- Etiology: majority are ***idiopathic (i.e. Ormond's Disease)***
    - Secondary etiologies: drugs, malignancy, autoimmune (e.g. lupus, ankylosing spondylitis), infection, radiation, chemotherapy, hemorrhage, aneurysm (inflammatory periaortitis), ***methysergide***, renal injury, hyper–immunoglobulin G4 syndrome
- Sx: Vague, dull pain is common; hypertension
    - Renal colic (ureteral obstruction), thrombosis (venous obstruction), lymphedema (lymphatic obstruction)
- Dx: biopsy – r/o secondary etiologies, particularly malignancy
    - Elevated ***ESR*** (erythrocyte sedimentation rate)
    - CT scan: fibrosis is most commonly seen surrounding infrarenal abdominal aorta and proximal common iliac arteries
        - ***Ureter medial displacement***
    - MRI: Acute phase – T2 high intensity; Chronic phase – T2 low intensity

- Tx: trial of ***corticosteroids***
    - Prednisone 40-60 mg/day for 2 months, taper to 10 mg/day, and continue treatment for 1-2 years if responding appropriately
        - May relapse after completion of steroid treatment
    - Secondary medications may be considered if inadequate response to steroids
        - Tamoxifen, azathioprine, mycophenolate mofetil
    - ***Ureterolysis*** – if severe hydronephrosis or inadequate response to medical treatment

CHAPTER 14: PEDIATRIC TUMORS

| CONGENITAL MESOBLASTIC NEPHROMA |

- Most common renal tumor of ***infants < 3-6 months***
- Benign tumor (rare malignant variant)
- Dx: asymptomatic abdominal mass; rarely ***HTN***; difficulty breathing secondary to diaphragmatic compression
- Tx: ***nephrectomy*** (unable to differentiate from Wilms' tumor)

Most Common Pediatric Abdominal Mass

Hydronephrosis

| WILMS' TUMOR (NEPHROBLASTOMA) |

- Most common pediatric renal tumor
- Mean age at diagnosis is 3.5 years old
- Wilms' tumor 1 (***WT1***) gene = chromosome ***11p13***
- ***WT2*** = chromosome ***11p15***
- Histology: ***Triphasic pattern*** (Blastema, Epithelium, Stroma) = classic
  - ***Nephrogenic rests***: considered "precursor Wilms tumor cells", and if present yields an increased risk of Wilms' tumor in the ***contralateral*** kidney
    - Intralobar nephrogenic rests are higher risk than perilobar

  - May be solid or cystic
  - Variants: Favorable (classic), anaplastic, or diffusely anaplastic
    - Most important prognostic factor; luckily, majority are favorable / classic histology

"Wilms' is the B.E.S.T." Mnemonic

Blastema, ***E***pithelium, ***S***troma (***T***riphasic pattern)

"Best" because high cure rate

- Dx: abdominal mass, pain, hematuria
  - ***Wilms' tumor does not cross midline*** (neuroblastoma does cross)
  - Patients with ***Wilms' tumor are well-appearing,*** while those with ***neuroblastoma are ill-appearing***

WILMS TUMOR STAGING (BASED ON SURGERY)

Stage	Description	Presentation % Approximation
1	Tumor confined within Gerota's fascia and completely resected	45%
2	Tumor not confined within Gerota's fascia; however it is completely resected	20%
3	Incomplete tumor resection, massive tumor spillage occurs, preoperative biopsy, or positive lymph nodes	20%
4	Distant metastasis	10%
5	Bilateral Wilms' tumor *	5%

** Bilateral tumors require renal biopsy and staging of each kidney*

- Tx: ***Radical nephrectomy*** with lymph node sampling and ***adjuvant chemotherapy*** (consider XRT if ≥ stage 3)
    - Neoadjuvant chemotherapy (***Vincristine, Dactinomycin and / or Doxorubicin***) for bilateral or unresectable tumors (i.e. vena cava tumor extension or large size), as well as tumors found in solitary kidney which may allow for a partial nephrectomy to avoid dialysis.
    - ***Most common complications***: small bowel obstruction, hemorrhage, wound infection or hernia
    - Abdominal / pulmonary external radiation may be of benefit in higher stages and anaplastic variants
- Prognosis: near 90% in localized disease and 70% of metastatic disease

DENYS-DRASH

- Wilms' tumor, DSD (gonadal dysgenesis – cryptorchidism, proximal hypospadias), Nephropathy (diffuse mesangial sclerosis)
- ***WT1*** gene (***11p13***)

WAGR SYNDROME

- **W**ilms' tumor, **A**niridia, **G**enitourinary abnormalities (hypospadias/ UDT), **R**etardation (mental)
- ***WT1*** gene (***11p13***)

BECKWITH-WIEDEMAN

- Macroglossia, gigantism, abdominal wall defects, Wilm's tumor association
- ***WT2*** gene (***11p15***)
- Approximately 10-15% have medullary sponge kidney

HEMIHYPERTROPHY

- Increased association with Wilms' tumor

NOTE: *Renal ultrasound every 3 months throughout early childhood for kids with Wilms tumor associated syndromes*

MULTICYSTIC DYSPLASTIC KIDNEY

- Increased association with Wilm's tumor; however, number needed to treat = 2,000, so prophylaxis is not feasible

| NEUROBLASTOMA |

- Majority present < 4 years old, approximately 1/3 prior 1 year old
- Origin: ***neural crest cells*** from the sympathetic nervous system
- Associated with ***N-myc*** gene mutation, and chromosome ***1p mutation***, which if present have a poorer prognosis
- Histology: ***small, round, blue cells*** with ***Homer-Wright pseudorosettes***
- Sx: abdominal mass that ***crosses midline***, children are ***ill-appearing***; may also be found in the posterior mediastinum
- Lab: ***only elevated norepinephrine*** (unable to convert to epinephrine because lack of PMNT, which is only in the adrenal medulla and pheochromocytomas)
    - o Urinary **VMA**
- Dx: biopsy, MIBG (if unclear), bone marrow aspiration (majority are positive)

NEUROBLASTOMA STAGING/TREATMENT

Stage	Description	Treatment
1	Localized tumor with **complete** excision	Excision
2A	Localized tumor with **incomplete** excision	Excision
2B	Localized tumor (no matter excision completeness) with **positive ipsilateral lymph nodes**	Excision
3	Unresectable tumor that **crosses midline** or **positive contralateral lymph nodes**	Chemotherapy then excision
4	Distant **metastatic disease** (e.g. bone marrow, liver, skin, bone)	Chemotherapy then excision
4S*	Localized tumor (1, 2A, 2B) with skin, liver and/or bone marrow metastatic disease, and **< 1 year old**	Spontaneous regression

** S = Special; only 5% of Neuroblastoma; their disease will usually spontaneously regress*

- Chemotherapy: cisplatin, doxorubicin, cyclophosphamide, etoposide
  - May be used at any stage
- **Pepper Syndrome**: extensive liver metastatic neuroblastoma (4S) that may lead respiratory failure
- **"Blueberry Muffin" Babies**: subcutaneous metastatic neuroblastoma (4S)
- **Hutchinson Syndrome**: bone metastasis resulting in limping and irritability in a young child
- **Horner's syndrome**: unilateral ptosis, miosis, and anhidrosis

| RHABDOMYOSARCOMA (RMS) |

- Most common pediatric soft tissue sarcoma; Majority seen in kids < 15 years old, with the remaining found in early adulthood
    - Bimodal distribution 6-10 then 18-20 years old
- Associated with Neurofibromatosis type 1, Beckwith-Wiedemann, Li-Fraumeni syndrome, Noonan syndrome
- Origin: ***rhabdomyoblasts***
- Histology: ***small, round, blue cells***
    - Stain positive for myoglobin, actin, desmin
- Variants: ***embryonal*** >> alveolar = undifferentiated sarcoma > botryoid
- Genitourinary involvement may occur in the prostate, bladder, para-testicular structures, vagina (***botryoid – grapelike clusters***), uterus, cervix
    - Prostate / bladder: poorer prognosis
- Imaging: MRI is study of choice
- Tx: multimodal – chemotherapy with radiation and/or surgical excision
    - Chemo: VAC (Vincristine, Actinomycin D, Cyclophosphamide)
- Prognosis: good for localized disease; poor for metastatic disease

RHABDOID TUMOR OF THE KIDNEY

- Rare tumor found in young children
- Previous thought rhabdomyosarcoma variant of Wilms' tumor; however, now identified as distinct renal tumor
- May have separate, primary, ***central nervous system tumors***
- Tx: nephrectomy, then chemotherapy
- Prognosis: highly lethal; rapid progression

| RENAL MEDULLARY CARCINOMA |

- Mean age of diagnosis is 11-13 years old
    - Usually metastatic at diagnosis
- Origin: ***collecting duct*** (different than collecting duct RCC)
- Seen almost exclusively in patients with ***sickle cell***
- High mortality rate, with median survival approximately 1 year

AGE OF PRESENTATION SUMMARY FOR PEDIATRIC TUMORS

Congenital mesoblastic nephroma	Neuroblastoma	Wilms' tumor	RMS	Renal medullary carcinoma
< 3-6 months	< 4 years	2-6 years	6-10 years	11-13 years

| MISCELLANEOUS |

CHILDREN WITH LARGE COMPLEX CYSTIC LESIONS

- DDx: cystic Wilms, multilocular cystic nephroma, congenital mesoblastic nephroma
- Tx: Nephrectomy, even though both of the nephromas are benign; unable to distinguish malignant from benign enhancing renal tumors.

MULTILOCULAR CYSTIC NEPHROMA (MLCN)

- Benign, unilateral, cystic tumor
- Bimodal distribution: young males (3 months – 4 years) and middle-aged females
- Sx: hematuria, abdominal mass
- DDx: cystic partially differentiated nephroblastoma (CPDN; intermediate tumor between MLCN and cystic Wilms tumor); cystic Wilms tumor
- Tx: nephrectomy (unable to differentiate from malignant cystic tumors on imaging)

CLEAR CELL SARCOMA OF THE KIDNEY

- Malignant renal tumor seen in young children
- ***Most common metastasis site: bone***
  - Formally known as the "bone metastasizing renal tumor of childhood"
- Usually large tumors (mean ~ 11cm)
- Tx: Nephrectomy then radiation and chemotherapy (vincristine, doxorubicin, cyclophosphamide, and etoposide)
- Prognosis: worse than Wilms tumor

Note: *Refer to Testicular Tumors Chapter regarding pediatric testicular malignancy.*

CHAPTER 15: PEDIATRIC UROLOGY

| PRENATAL ULTRASOUND |

AMNIOTIC FLUID

- **Polyhydramnios**: excess amniotic fluid in the gravid uterus
    - Ultrasound: ≥ 8cm pocket of fluid or amniotic fluid index ≥ 24
    - Overall fluid amount > 1.5 liters
    - Etiology: idiopathic (majority), gestational diabetes, neural tube defect, esophageal or duodenal atresia, volvulus
        - Gestational diabetes leads to premature labor and macrosomia in these patients
- **Oligohydramnios**: lack of enough amniotic fluid in the gravid uterus
    - Ultrasound: < 2cm pocket of fluid or amniotic fluid index < 5
    - Overall fluid amount < 0.5 liters
    - Etiology: renal agenesis, posterior urethral valves, PROM (premature rupture of membranes), fetal demise, genetic anomalies
    - May result in ***Potter sequence***: pulmonary hypoplasia, intrauterine growth retardation (IUGR), limb abnormalities, and Potter facies (low set ears, flat nose, micrognathia, prominent infraorbital folds)
    - Indications for in-utero urinary decompression:
        - Male, singleton fetus has bladder outlet obstruction
        - Oligohydramnios

- Favorable urinary indices for intervention
    - Low: sodium (< 100 mEq/L), chloride (< 90 mEq/L), osmolality (< 210 mOsm), and β_2-macroglobulin
- Otherwise normal fetus (normal karyotype, no systemic anomalies, non-cystic kidneys)
    - Fetal bladder puncture every 48-72 hours should demonstrate urine production (i.e. adequate renal function) and improvement of urinary indices

DEFINING ANTENATAL HYDRONEPHROSIS

Hydronephrosis	2nd Trimester AP* Diameter (mm)	3rd Trimester AP* Diameter (mm)	Risk of Underlying Pathology
Mild	4 to < 7	7 to < 9	~ 10%
Moderate	7 to < 10	9 to < 15	~ 50%
Severe	≥ 10	≥ 15	~ 90%

** AP = anterior-posterior renal pelvis diameter*

ETIOLOGY OF ANTENATAL HYDRONEPHROSIS

- Physiologic / transient hydronephrosis
- Ureteropelvic junction obstruction (UPJO)
- Vesicoureteral reflux (VUR)
- Ureterovesical junction obstruction (UVJO)
- Other: megaureter, multicystic dysplastic kidney, posterior urethral valves, ureterocele, prune belly syndrome, ectopic ureter, duplicated collecting system, urethral atresia

NOTE: *hydronephrosis is the most common abnormality seen on antenatal ultrasound.*

POSTNATAL MANAGEMENT OF ANTENATAL HYDRONEPHROSIS

Hydronephrosis	Imaging	When to Image	Antibiotics*
Mild	Renal U/S	1 month	No
Moderate	Renal U/S VCUG**	1 month	Yes
Unilateral – Severe	Renal U/S VCUG MAG-3	1 month	Yes
Solitary kidney or Bilateral – Severe	Renal U/S VCUG	1 week	Yes

** Amoxicillin 25mg/kg/day; may switch to Bactrim after 3 months (prior 3 months results in kernicterus)*

*** Proceed with VCUG, if persistent hydronephrosis on renal ultrasound or UTI while being observed.*

SFU* INFANT (POSTNATAL) HYDRONEPHROSIS

Grade	Description
0	No renal sinus splitting
1	Slight renal sinus splitting
2	Moderate renal sinus splitting (major calyceal dilation)
3	Wide renal sinus splitting (major and minor calyceal dilation)
4	Grade 3 with parenchymal thinning

** SFU = Society for Fetal Urology; Not accurate unless > 2 days of age due to relative dehydration; 1-2 = Low grade; 3-4 = High grade*

| URETEROPELVIC JUNCTION OBSTRUCTION (UPJO) |

- **Primary**
  - o ***Intrinsic***: inadequate peristalsis secondary to ureteral collagen deposition, decrease ureteral muscle, or mucosal folds
  - o ***Extrinsic***: external compression/kinking of the ureter by anteriorly crossing lower pole vessel
- **Secondary** UPJO secondary to vesicoureteral reflux, posterior urethral valves, or iatrogenic
- Associated with ***contralateral UPJO*** (10%), ***vesicoureteral reflux, renal dysplasia***
- Male > female; left > right kidney
- Dx: MAG3 renal scan with Lasix washout
  - o If split function 10-40% → pyeloplasty
  - o If < 10% split function and pain, recurrent infection, HTN, or significant proteinuria → nephrectomy
  - o If < 10% split function and pain-free or poor surgical candidate → observation
- Tx: ***dismembered pyeloplasty*** ~ 95% success rate (gold standard; particularly in pediatrics); other option is endopyelotomy (mild-moderate hydronephrosis, strictures < 2cm, no lower pole vessel, and good renal function)
  - o Indications: < 40% split function or delayed washout on a MAG-3 scan with furosemide, worsening hydronephrosis, decreasing GFR (> 10% decrease), renal AP diameter > 3cm, UTI
  - o ***Anderson – Hynes Repair***: common dismembered pyeloplasty technique; resection of obstructed portion with tension-free re-anastomosis
    - * Technique of choice for a crossing vessel – the ureter is transected and re-anastomosed anterior to the vessel
  - o ***Foley Y-V plasty***: optimal for high ureteral insertion
    - * Crossing vessel is a contraindication
  - o ***Ureterocalicostomy***: indicated in failed pyeloplasty, intrarenal pelvis or long stricture
  - o Maintain ureteral stent 4-6 weeks

| URETEROVESICAL JUNCTION OBSTRUCTION |

- Ureteral obstruction at the level of the bladder resulting in hydroureteronephrosis
- **Primary**: inadequate smooth muscle within the intramural ureter (i.e. adynamic segment) resulting aperistalsis
- **Secondary**: external ureteral compression by a thickened bladder wall
- Male > female; left > right kidney
- Associated with ***contralateral agenesis, ipsilateral VUR***
- Dx: need VCUG to rule out VUR
- Tx: if primary and asymptomatic etiology, usually self-limiting; however, will need prophylactic antibiotics (UTI risk)
    - o ***Ureteroneocystostomy***: recurrent UTI, decreased GFR, worsening hydronephrosis, nephrolithiasis
        - * ***Post-operative edema is common. If 8 week post-operative renal ultrasound still has hydronephrosis, observe and check MAG-3 in 1 month.***
            - If edema is symptomatic, consider stent or nephrostomy

Ureteroneocystostomy

5:1 ratio of ureteral tunnel length to diameter

Taper the distal ureter, if > 1.75 cm diameter

- o Secondary etiology: correct underlying etiology resulting in bladder thickening (e.g. posterior urethral valves incision)

| POSTERIOR URETHRAL VALVES (PUV) |

- Urethral, congenital, obstructing membrane arising from the verumontanum causing bladder outlet obstruction

  - Mesonephric (Wolffian) ducts abnormal integration into the cloaca anteriorly, rather than posteromedial, resulting in fusion of the plicae colliculi (posterior urethral folds)
- Categories
  - **Type 1 Classic PUV** (95%): membrane originates from the lateral border of verumontanum and join at 12 o'clock
  - **Type 2:** Membrane originates from the verumontanum and extends towards the bladder neck
  - **Type 3**: Circular diaphragm with a central defect (similar to membrane with hole in the middle)
- **COPUM**: congenital obstructing posterior urethral membrane
  - Theory that there is only one type of PUV, which is a persistent oblique membrane that has different rupture patterns upon catheterization / instrumentation.
- Dx: antenatal ultrasound: bilateral hydronephrosis with ***keyhole sign*** (dilated bladder and posterior urethra), oligohydramnios, thickened bladder wall
  - **VCUG**: Bladder wall thickening and trabeculation, dilated posterior urethra
- Tx: ***immediate postnatal catheterization*** in boys with bilateral antenatal hydronephrosis
  - ***Primary valve ablation*** – gold standard treatment
  - ***Vesicostomy*** – unable to instrument secondary to urethral caliber
  - ***Cutaneous ureterostomy*** – rare, consider if increasing creatinine despite adequate bladder drainage
  - If VUR persists after treatment, consider reimplantation only if bladder function returns to normal
- Prognosis is best if Cr nadir is < 0.8 (Cr > 1 has increased risk of ESRD)
  - ~ 25% will progress to ESRD in their lifetime
- Postoperative findings from previous bladder outlet obstruction
  - Most commonly ***overactive bladder*** / detrusor instability / decreased compliance → timed voids, anticholinergics

    - If polyuria from concentrating defect (***nephrogenic diabetes insipidus***), consider nocturnal catheter drainage
  - Decreased detrusor contraction (***detrusor myogenic failure***) → timed voids, CIC, alpha blocker
    - Catheterization may be difficult secondary to a hypertrophied bladder neck

| PRUNE BELLY SYNDROME (PBS) |

PBS = TRIAD SYNDROME = EAGLE-BARRETT SYNDROME

- 95% are males; more common in twins and African-American babies
- Etiology: unclear
- ***Abdominal musculature deficiency***
- ***Bilateral cryptorchidism***
  - Usually at level of iliac vessels
- ***Urinary tract anomalies*** (e.g. hydronephrosis, ***renal dysplasia***, dilated prostatic urethra, enlarged bladder, VUR, patent urachus ~ 25%)
  - ***Usually non-obstructive hydronephrosis***
  - Massively dilated, collagen-laden bladder with a wide bladder neck and dilated prostatic urethra (secondary to ***prostatic hypoplasia***)
    - Normal compliance usually (~ 50% have normal voiding pressure / uroflow rates)
  - May have a ***prostatic utricle*** – invagination seen at the verumontanum (Mullerian duct remnant representing the vagina)
    - May make CIC difficult

Diseases Associated with a Prostatic Utricle

Mnemonic – H.E.A.D.

*H*ypospadias

*E*agle-Barrett Syndrome

*A*nus is imperforate

*D*owns syndrome

- The anterior urethra is usually normal, but may have atresia or megalourethra
    - o ***Atresia***: must have patent urachus to survive
    - o ***Megalourethra***
        - * ***Scaphoid***: lacks corpus spongiosum
            - Ventral phallic dilation with urinating
        - * ***Fusiform***: lacks corpus cavernosum and spongiosum
            - Entire phallus dilates with urinating
            - Extremely rare
- Usually normal secondary sexual characteristics; however, likely infertile
- ~ 75% have extra-genitourinary abnormalities as well
    - o Abdominal muscle deficiency
        - * Skin, subcutaneous fat, peritoneum only
    - o ***Pulmonary hypoplasia*** – severe oligohydramnios
    - o Volvulus
    - o Orthopedic abnormalities – oligohydramnios results in limb compression
- ***Prenatal death occurs in ~ 20% of PBS (40% if female)***
- Spectrum of PBS secondary to variability of abnormalities. Treatment is based on severity of spectrum. The most severe forms usually die early, while the least severe form may benefit from orchidopexy

and observation. Treatment for the intermediate spectrum PBS is controversial.

- Treatment: supravesical urinary diversion if renal failure
    - o DVIU – does not result in incontinence in PBS!
    - o Reduction cystoplasty
    - o Urethral reconstruction
    - o Orchidopexy
    - o Abdominal wall reconstruction (Monfort and Ehrlich techniques)
    - o Monitor Creatinine
        - * ***If Cr nadir as infant is < 0.7, good prognosis for renal function, unless issues with pyelonephritis***

| VESICOURETERAL REFLUX (VUR) |

- **Primary**: insufficient submucosal ureteral tunnel or ectopic ureteral insertion (i.e. not within the trigone)
- **Secondary**: bladder abnormality
- Heredity
    - o 100% in identical twins
    - o ~ 1/3 of siblings and offspring

Sibling / Offspring VUR Screening

Consider a renal ultrasound, and if renal scarring is present or history of UTI then proceed with a VCUG

- ***VUR consequences***: pyelonephritis / UTI, renal scarring, reflux nephropathy (non-infectious renal damage), decreased GFR
    - o ***Reflux nephropathy leads to hypertension*** (Tx: ACE inhibitor)
- ***VUR associated anomalies***: UPJO, ureteral duplication (lower renal unit), bladder diverticulum, renal agenesis, multicystic dysplastic kidney, VACTERL, CHARGE

- Dx: ***VCUG*** is gold standard imaging study for VUR diagnosis
    - DMSA evaluates for renal scarring

VUR GRADING ON VCUG

Grade	Description
1	Reflux within the ureter only
2	Reflux to the kidney without dilation
3	Reflux to the kidney with mild dilation
4	Reflux to the kidney with moderate dilation
5	Reflux to the kidney with severe dilation and ureteral tortuosity

DMSA indications

Abnormal renal ultrasound; VUR grades 3-4; breakthrough UTI on antibiotics; rising creatinine; baseline renal scarring if history of febrile UTI

- Treatment:

APPROXIMATE SPONTANEOUS VUR RESOLUTION RATES

Grade 1-2	Grade 3	Grade 4-5
80%	50%	20%

- **Child < 1 year of age with VUR**
    - Overall ~50% will resolve spontaneously in < 1-2 years
    - Males → circumcision (decreases UTIs)
        - If bilateral in males, suspect bladder outlet obstruction, and check a VCUG to rule out PUV.

- If grade 1-2, follow up at 1 year with VCUG
- If history of febrile UTI or VUR grade 3-5→ continuous antibiotic prophylaxis
    - Follow up VCUG in 1 year

Child > 1 year of age with VUR

- Screen for concurrent bladder/bowel dysfunction (BBD), and treat prior any surgical intervention
    - If BBD (increased UTI risk) → continuous antibiotic prophylaxis
- If UTI and not on antibiotics, consider starting continuous antibiotic prophylaxis
- If breakthrough UTI on antibiotics, consider surgical intervention (i.e. ureteral reimplant or endoscopic ureteral bulking injection)
- Be suspicious of bladder/bowel dysfunction

VUR Surgical indications

Breakthrough UTI on antibiotics; non-compliance; VUR Grades 4-5; worsening renal function; new renal scars on DMSA; stagnant renal growth

Surgery

- Extravesical: Lich-Gregoir
- Intravesical: Politano-Leadbetter, Cohen cross-trigonal, Glenn-Anderson

Endoscopic

- Hyaluronic acid and dextranomer microsphere (Deflux®) submucosal ureteral orifice injection

Post-operative Follow Up

- Renal ultrasound at 6-8 weeks
    - If tapered ureteroneocystostomy, expect continued hydronephrosis from significant edema for several weeks

- VCUG at 3-6 months
    - Continue prophylactic antibiotics until normal VCUG
- Annual physical, UA (rule out proteinuria and UTI), and blood pressure. If any abnormalities → renal ultrasound and/or VCUG.

| HYPOSPADIAS |

- Congenital urethral abnormality with the urethral meatus proximal to the tip of the glans; may have associated ***chordee*** (ventral penile curvature)
    - Failure of urethral plate fusion
    - ***Dorsal hood***: common; incomplete prepuce ventral
    - The more proximal the greater risk for disorder of sexual differentiation

HYPOSPADIAS LOCATION

Classification	Location	Incidence
Anterior / Distal	Glanular	~ 50%
	Coronal	
	Subcoronal	
Middle	Distal penile	~ 20%
	Midshaft	
	Proximal penile	
Posterior / Proximal	Penoscrotal	~ 30%
	Scrotal	
	Perineal	

- Embryology: normal urethral formation occurs from proximal to distal direction; the normal urethral meatus occurs with glanular epithelial invagination
    - Hypospadias may have a blind ending pit/dimple at the tip of the glans
- Incidence: 0.4% of live male births
- ***Rule of 10's*** (Approximate incidence of hypospadias associations)
    - 10% of siblings have hypospadias
    - 10% of offspring have hypospadias
    - 10% have an ***undescended testicle*** (~1/3 in penoscrotal hypospadias)
    - 10% have an ***inguinal hernia***
    - 10% of proximal hypospadias patients have a ***prostatic utricle***

Karyotype

Required if proximal hypospadias and undescended testicle

- Treatment: surgical intervention between 6-18 months
    - o ***Meatal advancement and glanuloplasty procedure (MAGPI)***
        - * Distal hypospadias repair
    - o ***Thiersch-Duplay:*** urethral plate tubularization
        - * May not have adequate lumen diameter
    - o ***Tubularized incised plate (TIP; Snodgrass):*** posterior urethral plate incision, then urethral plate tubularization
        - * Commonly used for distal hypospadias
    - o ***Preputial onlay island flap***: prepuce (i.e. dorsal hood) is used as only flap to reconstruct the urethra
    - o May require multiple staged repairs or buccal mucosal grafts for severe/proximal hypospadias (see Urethral Disease chapter for buccal mucosal graft discussions)
    - o ***Byars' flaps***: rotation of the dorsal prepuce to cover the ventral shaft after hypospadias or chordee repair
- Surgical Complications
    - o **Urethrocutaneous fistula**: observe for 6 months (may spontaneously close), prior to surgical repair
    - o **Meatal stenosis**
    - o **Urethral diverticulum** – usually secondary to meatal stenosis
    - o **Urethral stricture** – usually secondary to urethral plate / flap ischemia
    - o **Chordee** – persistent or de novo

| CRYPTORCHIDISM |

- ***Cryptorchidism***: hidden or obscure testicle (broad, all-inclusive term)
- ***Undescended testicle (UDT)***: testicle fails to descended into the normal, dependent position within the scrotum
    - Abdominal (retroperitoneal), inguinal, prescrotal, high scrotal
- ***Ectopic testicle***: testicle is located in an abnormal position, not along the normal path of descent
    - Penile, retrovesical, femoral, perineal
- ***Retractile testicle***: testicle has descended properly; however, a brisk cremaster reflex results in retraction of the testicle into the inguinal canal
    - Suspect if scrotum is fully developed
    - Monitor annually until puberty; majority are self-limiting, but may become scarred in the retracted position
- Incidence: undescended testicles occur in ~ 3-4% of full term male births (up to 30% in preterm infants)
    - < 1% by 1 year of age (rarely resolves after 1 year of observation)
    - Up to 15% have bilateral UDT (will need karyotype)
- Etiology: multifactorial: premature birth, low birth weight, family history, abnormal gubernaculum formation, abnormal hypothalamic-pituitary-gonadal axis, lack of 5-alpha-reductase, disorders of sexual differentiation
    - Testicles normally descend into the scrotum between 28-40 weeks
- ***Testicular cancer***: increased overall risk associated with cryptorchidism. See the Testicular Tumor Chapter for further details.

Undescended Testicles and Infertility

Unilateral UDT: unchanged fertility rate

Bilateral UDT: ~ 2/3 fertility rate

- Treatment: ***orchidopexy*** at 6-12 months of age
  - If found to have a scrotal nubbin (testicular vessels and vas deferens enter a closed inguinal ring), may leave the nubbin within the scrotum as there is not an increase in malignant potential. If any concern, may remove it from a scrotal approach.
    - The contralateral testicle will have compensatory hypertrophy
  - Palpable UDT: inguinal approach
  - Non-palpable UDT: inguinal vs. laparoscopic approach (physician preference)
    - Do not need a preoperative ultrasound prior to exploration
  - ***Prentiss maneuver***: technique to give more cord length by dividing the epigastric vessels – allows for the cord to be moved medially and lie more dependent in the scrotum
  - ***Fowler- Stephens procedure***: 2-staged procedure to allow further testicular mobilization
    - Stage 1: division of gonadal vessels
    - Stage 2: awaiting for collateral testicular vessels to mature, and then perform the orchidopexy

CRYPTORCHIDISM TREATMENT

Age	Overall Health (ASA score)	Treatment
< 10-12 (prepubertal)	---	Orchidopexy
12 - 50	ASA 1 or 2	Orchiectomy
12 – 50	ASA 3 or 4	Observation
> 50	---	Observation

| TESTICULAR TORSION |

EXTRAVAGINAL TORSION

- Ischemic rotation of the entire spermatic cord secondary to the tunica vaginalis not adhering to the gubernaculum yet.
- 5% of all testicular torsions
- Most commonly an ***antenatal event***, thus seen in neonates
- Non-tender, hard, solid testicular mass
- Tx: contralateral orchidopexy in first week of life

INTRAVAGINAL TORSION

- ***Bell clapper deformity*** (high attachment of the tunica vaginalis) allows the spermatic cord to rotate within the tunica vaginalis
- Most commonly an ***adolescent event***
  - o Testicular volume ***≥ 4 cm³*** indicates the beginning of puberty
- Tender, horizontal testicular lie, loss of cremasteric reflex
- Dx: clinical diagnosis
  - o Testicular Doppler ultrasound: lack of intratesticular blood flow with increase peripheral flow (***ring of fire***), heterogeneous testicle (necrosis)
- DDx: epididymo-orchitis, testicular mass, testicular appendage torsion
  - o ***Prehn's sign***: positive if testicular elevation relieves pain, and

suggests epididymo-orchitis

  - ***Blue dot sign***: tender superior pole nodule with bluish scrotal dot
- Tx: emergent scrotal exploration with ipsilateral detorsion with orchidopexy vs. orchiectomy and contralateral orchidopexy
  - During exam, may try manual detorsion while awaiting operative procedure, which results in immediate decrease in pain
    - ***Open book rotation***: rotate the testicle medially to laterally
  - Surgery within 6 hours: 90% salvage rate
  - Surgery after 24 hours: ~ 0% salvage rate

Testicular Torsion Presentation

Testicular pain, nausea, pubic hair present (high sensitivity for torsion)

| NEURAL TUBE DEFECTS |

- ***Spina bifida:*** incomplete spinal closure (usually lumbosacral region)
  - Fertility associated with ≤ L5 defect
  - May have sacral dimple or tuft of hair
- ***Meningocele***: meninges protrude through the spinal defect
- ***Myelomeningocele***: meninges and spinal cord / nerve roots protrude through the spinal defect
- Workup: urinary dynamic study, renal ultrasound
  - Majority will have a ***neurogenic bladder***
  - VUR in ~ 50%
  - Many spina bifida patients are ***allergic to latex*** (including anaphylaxis)

- Treatment:
    - o ***Detrusor overactivity or noncompliant bladder***: anticholinergic + CIC
        - * Vesicostomy may be used for infants to protect the upper tracts
        - * Augmentation cystoplasty or Mitrofanoff appendicovesicostomy may be consider for long-term management
    - o ***Areflexic bladder***: CIC
    - o ***Neurogenic bowel***: may consider an ***antegrade continence enema (ACE)*** – Malone ACE utilizes the appendix as catheterizable channel to the cecum
        - * A colorectal stoma that allows for administration of an enema
        - * Complications: stomal stenosis (~1/3) → revise, cecostomy tube insertion; colonic washout failure within 2 hours → may require a diverting colostomy or if right colonic ACE, may need left colonic ACE or colonic tube (avoids diverting colostomy)
        - * ***Maximal liters of ACE irrigant fluid = 0.035(kg)***
            - Exceeding this amount may lead to sodium variation
        - * May use polyethylene glycol; however, may lead to clostridium difficile
    - o ***VUR***: treat underlying bladder pathology (usually secondary to increased intravesical pressure). Prophylactic antibiotics are needed if VUR.

Asymptomatic Bacteriuria

Does not require prophylactic antibiotics

ANTENATAL DIAGNOSIS

- ***Alpha-fetoprotein (AFP)***: elevated if fetus has neural tube defect
- ***Antenatal Ultrasound***: high sensitivity and specificity when elevate AFP

| MISCELLANEOUS |

PHIMOSIS

- Inability to retract the prepuce
- Congenital phimosis is normal, and the prepuce-glanular adhesions will breakdown naturally with time and tumescence. Parents should not try to retract the prepuce.
- If pathologic (usually in adults) → topical steroid ointment; circumcision or dorsal slit

PARAPHIMOSIS

- Preputial strangulation of the penile glans
- Requires urgent manual reduction or dorsal slit to avoid permanent ischemic damage

PEDIATRIC CONTINENCE SEQUENCE

- Nocturnal fecal continence
- Diurnal fecal continence
- Diurnal urinary continence
- Nocturnal urinary continence

NOCTURNAL ENURESIS

- Bedwetting
- Incidence: 15% of 5 year olds, 5% of 10 year olds, 1% of 15 year olds
- Tx: no requirement for treatment; treat based on distress of child or parental desire once 7 years of age
  - o ***Nocturnal enuresis alarm*** (highest success rate and lowest relapse rate)
  - o ***DDAVP (Desmopressin***®, ADH***)***: 0.2-0.6mg orally or 10-40μg intranasal nightly
    - * Reduces nightly urine production
    - * High relapse rate; however, may be used while awaiting spontaneous resolution
  - o ***Anticholinergics***: only helpful if daytime urgency/frequency

DYSFUNCTIONAL ELIMINATION SYNDROME (DES)

- Constipation that commonly leads to daytime wetting, voiding complaints, elevated post-void residuals, UTI and encopresis
- ***If a child has NEW voiding complaints, have a high suspicion for constipation / DES***
- Tx: polyethylene glycol 3350 (MiraLAX®), timed voiding, biofeedback

CUTANEOUS URETEROSTOMY

- Indicated for infants with an obstructed, functional kidney that are to ill or premature for reconstructive procedures

NEWBORN CREATININE

- Reflects the maternal creatinine for the first 48-72 hours of life

URETEROCELE: *see Genital Anomalies Chapter for further details*

CHAPTER 16: BLADDER PHYSIOLOGY AND NEUROGENIC BLADDER

| CENTRAL MICTURITION CONTROL |

CEREBRAL CORTEX

- Provides voluntary control to void
- ***Right dorsolateral prefrontal cortex*** (particularly the orbitofrontal) and ***anterior cingulate gyrus*** are important for voluntary voiding
- Other areas of the brain involved: periaqueductal gray (midbrain), thalamus, insula, and hypothalamus all play a part in normal micturition

PONTINE MICTURITION CENTER (PMC)

- ***Medial PMC (Barrington's nucleus)***: results in ***voiding*** via the sacral micturition center and stimulation of the sacral parasympathetic nerves
- ***Lateral PMC***: results in ***bladder storage*** via the sacral micturition center and stimulation of the thoracolumbar sympathetic nerves

SACRAL MICTURITION CENTER

- ***Voiding***: stimulates sacral parasympathetics, while inhibiting the sympathetics and somatic nerves
- ***Storage***: inhibits parasympathetics, while stimulating sympathetics and somatic nerves
    - ***Guarding reflex***: urethral reflex to maintain continence during bladder filling via the pudendal nerve. May also have input from lateral PMC.

  - o ***Sacral reflex***: afferent signals to the sacral micturition reflex initiate detrusor contraction without suprasacral input. Traditionally thought to be infant voiding pathway, and may return in certain pathologic conditions.
  - o ***Urethral-Bladder reflex***: urine flows into the urethra resulting in a detrusor contraction via pudendal stimulation of the PMC or pelvic nerve stimulation of the SMC. The urge component of mixed incontinence in females may be a result of this reflex, and may be ultimately corrected with a mid-urethral sling.

| PERIPHERAL MICTURITION CONTROL |

PARASYMPATHETIC

- Stimulation results in bladder contraction to aid in bladder emptying
- Origin: S2-S4 spinal segments
- Plexus: Inferior hypogastric plexus
- Nerve: Pelvic nerves
- Receptors: ***Muscarinic-3 (M3) receptor*** stimulation via ***acetylcholine*** is main pathway for detrusor contraction
  - o There are more M2 receptors than M3; however, M3 is most important for detrusor contraction
- Parasympathetic postganglionic nerves also release ***ATP*** and ***nitric oxide***, which stimulates ***detrusor contraction*** via P2X purinergic receptors and ***relaxes urethral smooth muscle, respectively.***

Urothelium Receptors

The urothelium contains muscarinic and nicotinic receptors as well. This is the basis for intravesical treatment of overactive bladder.

SYMPATHETIC

- Stimulation results in bladder relaxation and bladder neck contraction to aid in bladder storage; inhibited for micturition
- Origin: T11-L2
- Plexus: Pelvic plexus
- Nerve: Hypogastric nerve
- Receptors: Beta-3 (β-3) on the detrusor and Alpha-1 (α-1) receptor on the bladder neck and trigone are stimulated via norepinephrine

SOMATIC

- Stimulation results in external urethral sphincter contraction; voluntary control
- Origin: S2-S4
- Nucleus: ***Onuf's nucleus*** within the sacral ventral horn
- Nerve: Pudendal nerve
- Receptors: Nicotinic receptor stimulation via acetylcholine

Bulbocavernosus Reflex

Squeezing the glans penis / clitoris or gently tugging on a Foley catheter should produce anal sphincter contraction

Tests ***S2-S4*** nerve roots

AFFERENT NERVES

- ***Myelinated alpha-delta (αδ) fibers***: afferent nerves that respond to bladder stretching (i.e. bladder fullness) and send this information to the sacral and pontine micturition centers, which is transmitted to the periaqueductal gray and cerebral cortex
    - ***Micturition Reflex*** is a ***spinobulbospinal reflex*** that is initiated by an intense stimulation to void due to bladder distention / filling
        - This may be inhibited in adults and young children (~3 years old) by the cerebral cortex to a socially acceptable situation

- ***Unmyelinated capsaicin-sensitive (C) fibers***: silent afferent nerves under normal situations; however, they may become stimulated with noxious stimuli (e.g. cool water irrigation).
  - o Pathologic C-fiber stimulation of micturition reflex may also be seen in neurogenic detrusor overactivity and bladder pain syndromes

BLADDER

- Storage and emptying phases depend on the neurologic system as well as the intrinsic properties of the urinary bladder
- **Compliance = Δ volume / Δ pressure**
- ***Laplace's Law*** is bladder wall tension ≈ detrusor pressure x bladder radius
- During bladder filling, the intramural ureteral pressure and contraction frequency increase

ANATOMY

- Bladder = urothelium + lamina propria + muscularis propria + adventitia / serosa
  - o ***Urothelium layers***: GAG - Uroplakins (apical membrane) - umbrella cell - intermediate cell - basal cell

Urothelium Thickness

Relaxed: 5-7 cell layers thick

Distended: 2-3 cell layers thick

  - o ***Interstitial cells (of Cajal) - myofibroblasts***
    - * Located within the lamina propria and detrusor
    - * Function as "bladder pacemaker cells" with neurologic interaction
    - * May be upregulated in overactive bladder
  - o ***Lamina***
    - * Composed of collagen (~50% of bladder wall) and elastin

    - Increased collagen = less compliance
    - Aging results in increased collagen (particular type 3), thus decrease compliance
  - ***Muscularis propria***
    - Smooth muscle (~50% of bladder wall)
    - Bladder outlet obstruction and detrusor denervation leads to increase smooth muscle (i.e. detrusor hypertrophy)
  - ***Adventitia***: connective tissue
  - ***Serosa***: peritoneal layer found at bladder dome
- ***Internal sphincter***: involuntary, smooth muscle at the bladder neck
- ***External rhabdosphincter***: voluntary skeletal muscle
  - Male: distal to prostate apex at membranous urethra
  - Female: stretches from the proximal to distal urethra

Kegel Contraction

Isometric exercise of the pubococcygeus muscle

DETRUSOR CONTRACTION

- M3 receptor or P2X receptor stimulation → Calcium entry through nifedipine sensitive L-type calcium channels along with inositol triphosphate activation → sarcoplasmic reticulum release of calcium stores → Calmodulin-calcium complexes form → activates myosin light-chain kinase → phosphorylation of myosin type 2 light chain → interacts with actin → detrusor contraction
- Detrusor myocytes stretch with bladder filling, and raises the membrane resting potential (i.e. less negative). This allows for easier detrusor activation by the parasympathetic system.
- ***Caffeine***: sensitizes the sarcoplasmic reticulum to release calcium stores (i.e. less calcium entry need for detrusor contraction), which may result in spontaneous contractions
- Complete detrusor contraction is critical for bladder emptying. If an area does not contract at the same time, the increased pressure

leads to a focal increase in compliance that ultimately results in a ***diverticulum***.

- ***Bladder decompensation***: as the bladder fills with increasing intramural tension, blood flow decreases to the bladder cells. This hypoxia leads to a rapid decrease in detrusor contractility.

NEUROLOGIC VOIDING PATHWAYS

- **Normal voiding**: Detrusor ***αδ fibers*** afferent input → suprasacral spinal tract neurons → periaqueductal grey → pontine micturition center and cerebral cortex → sacral spinal micturition center → parasympathetic activation + sympathetic inhibition → detrusor contraction
- **Spinal reflexive voiding** (pathologic voiding): Detrusor ***C fibers*** afferent input → sacral spinal micturition center → parasympathetic activation + sympathetic inhibition → detrusor contraction

| PATHOLOGIC VOIDING |

SUPRAPONTINE LESIONS

- The prefrontal cortex loses the periaqueductal gray tonic suppression over the pontine micturition center
    - o Gamma-Aminobutyric acid (GABA) is the inhibitory neurotransmitter
- Decreased bladder capacity, detrusor overactivity, detrusor sphincter synergy is maintained
- Examples: cerebral infarct / tumor, Parkinson's Disease, multiple sclerosis

SUPRASACRAL - SPINAL CORD INJURY (PMC TO S1 NERVE ROOT)

- ***Spinal Shock:*** flaccid, areflexic bladder seen immediately post-SCI
    - o Usually lasts 2-3 months
- Involuntary voiding (i.e. no supraspinal input) occurs via the ***sacral reflex (C-fibers)*** once spinal shock has resolved. Voiding is usually inadequate secondary to development of ***detrusor sphincter dyssynergia***.

- Lack bladder sensation
- May lead to vesicoureteral reflux, so monitor upper and lower tracts annually
- Examples: spinal fracture, multiple sclerosis
- **Autonomic Dysreflexia**
    - Patients with a spinal cord injury at ***T6 or above*** may respond to a stimulus (e.g. bladder or bowel distension) with profound autonomic overactivity resulting in ***hypertension, reflexive bradycardia***, ***diaphoresis***, facial flushing, altered mental status, and headache.
    - The sympathetic nervous system is stimulated, which causes systemic vasoconstriction. Reflexive parasympathetic signals attempt to counter the vasoconstriction, but are impeded by the high thoracic spinal injury. The sympathetics below the level of injury continue to vasoconstrict, while the parasympathetics above the injury level result in bradycardia.
    - ***Tx: immediately remove inciting stimulus; immediate-release Nifedipine; nitrates***

Nerve vs. Vertebral Levels

The S2 nerve root (sacral lesions) is anatomically located at the L2 vertebra and below (i.e. cauda equina)

SACRAL AND INFRASACRAL LESIONS (≤ S2 NERVE ROOT)

- Loss of normal and pathologic voiding reflexes results in a ***flaccid, areflexic bladder***
- Open internal sphincter with contracted external sphincter
- Lack bladder sensation
- Examples: sacral fracture, spinal stenosis, myelodysplasia, tethered cord, anterior horn damage (Polio, Herpes zoster, surgical injury)

SUMMARY OF URODYNAMIC FINDINGS IN CNS LESIONS

Findings	Suprapontine	Suprasacral	Sacral
Detrusor	Overactive	Overactive	Areflexic
Sphincter	Synergy	DSD	Contracted
Sensation	Present	Absent	Absent

DSD = detrusor sphincter dyssynergia

OVERACTIVE BLADDER (OAB) VS. DETRUSOR OVERACTIVITY (DO)

- ***Overactive bladder***: clinical finding of ***urgency***, frequency, nocturia
    - Dry: no associated urge incontinence
    - Wet: associated urge incontinence
- ***Detrusor overactivity***: urodynamics finding of involuntary detrusor contractions during the filling phase
    - Idiopathic: non-neurologic etiology
    - Neurogenic: neurologic etiology

| NEUROGENIC BLADDER (NGB) |

PARKINSON'S DISEASE

- Lose of pigmented, dopaminergic neurons in the substantia nigra (midbrain) results in bradykinesia, pill-rolling tremor, cogwheel rigidity, masked facies, and shuffling gait.
- Most common associated NGB is ***neurogenic detrusor overactivity*** with ***impaired contractility***
- ***"Pseudo-DSD"***: bradykinesia of the external sphincter results in a condition similar to DSD, such as urinary retention, low urine flow
- Bladder sensation is intact
- TURP is a relative contraindication in patients with Parkinson's disease because of the high incidence of post-TURP urinary incontinence (~ 20%).

- Tx: anti-cholinergic ± CIC

SHY DRAGER SYNDROME

- Multiple systems atrophy = Parkinsonism + autonomic dysfunction
- Urinary dysfunction is commonly diagnosed several years prior to neurologic diagnosis
- Bladder overactivity with poor compliance and contraction; open bladder neck; external urethral sphincter denervation; urinary retention common
- TURP will likely result in post-TURP urinary incontinence
- Tx: anti-cholinergic ± CIC

PARKINSON'S VS. SHY DRAGER NEUROGENIC BLADDER

UDS Findings	Parkinson's Disease	Shy Drager Syndrome
Bladder Neck	Closed	Open
Bladder Compliance	Normal	Decreased
Bladder Reflex	Hyperreflexia	Hyporeflexia
Sphincter	Bradykinesia	Denervated
Autonomic dysfunction	Absent	Present

CEREBRAL VASCULAR ACCIDENT

- May have initial spinal shock-like episode of urinary retention; however, the patient will usually have ***neurogenic detrusor overactivity*** within 6-12 weeks
- Bladder sensation and compliance are normal
- Tx: initially: may need CIC; long-term: may need anti-cholinergics

MULTIPLE SCLEROSIS (MS)

- Central nervous system demyelinating disease that impairs nerve conduction. It is usually relapsing and remitting; however, may become progressive.

- Majority of MS patients will have voiding difficult at some point
- Most common is ***neurogenic detrusor overactivity***
    - Voiding issues frequently resolve / change, and may result in urinary retention from decreased detrusor contraction or DSD
- Bladder sensation is present in vast majority
- Tx: treat primary symptom; however, monitor for elevated urinary tract pressures that could lead to upper tract deterioration

SPINAL STENOSIS

- Spinal column narrowing with compression of the spinal cord and nerves resulting in back pain with claudication
- Variable urodynamic and clinical findings that range from overactivity to areflexia
- Tx: neurosurgical decompression has variable success

TETHERED CORD

- The spinal cord should normally free float in cerebrospinal fluid. It can have abnormal cord attachments or tightness that results in cord immobility. The immobility ultimately results in ***hypoxic nerve damage***.
- Bladder/bowel retention or incontinence; lower extremity pain, weakness, and numbness
    - 1/3 will present with a urologic issue
- Dx: clinical suspicion with MRI
    - NOTE: MRI post-surgery will not illustrate re-tethering; may require routine urodynamics to evaluate for recurrence
- Tx: neurosurgical tethered cord release
    - ~20% will recur

Conus Medullaris

Terminates near the vertebral level of L3 as an infant, and ascends to the L1-L2 area as an adult

CAUDA EQUINA SYNDROME

- Acute compression of the spinal cauda equina (lumbosacral nerve roots) that requires emergent neurosurgical decompression
    - o Majority of disc protrusions occur posterolateral; however, a central protrusion is usually need to compress the cauda equina
- Sx: lower motor neuron findings; decreased reflexes; saddle paresthesias; urinary retention; radicular pain; muscle weakness; asymmetric lower extremity findings; erectile dysfunction
- Dx: check anal sphincter tone, bulbocavernosus reflex, extremity reflexes; urgent MRI (consider in all new onset urinary retention or incontinence with concomitant back pain)
    - o UDS: bladder areflexia
- Tx: Neurosurgical decompression

SUMMARY OF NEUROLOGIC TESTING

Nerve Root (Disc)	Reflex	Motor	Sensory
L4 (L3/4)	Patellar DTR	Ankle dorsiflexion	Medial malleolus
L5 (L4/5)	n/a	Great toe dorsiflexion	Dorsal foot
S1 (L5/S1)	Achilles DTR	Ankle plantar flexion	Lateral malleolus, Heal
S2-4	Bulbocavernosus	Rectal tone	Perineum, genitals

DIABETIC CYSTOPATHY

- ***Sensory neuropathy*** leads to delayed first sensation during filling, which results in elevated filling volumes. This ultimately leads to decreased contractility and incomplete emptying (i.e. large, flaccid bladder that lacks sensation).
- Patients usually have decreased vibratory sensation in the hands and feet

- Urodynamics: decreased sensation and contractility; increased capacity and post-void residual
- Tx: improved glucose control; timed voiding ± CIC; Bethanechol

TABES DORSALIS (NEUROSYPHILIS)

- Untreated Treponema pallidum may lead to demyelination of the ***dorsal columns and posterior nerve roots*** that results in decreased sensation (proprioception, vibratory sensation, discriminative touch)
- ***Sensory neuropathy*** leads to a lack of bladder sensation with urinary retention and incomplete voiding
- Tx: Aqueous crystalline Penicillin G 18-24 million units/day divided over 6 doses for 10-14 days; timed voiding ± CIC

PERNICIOUS ANEMIA

- Megaloblastic anemia caused by vitamin B12 deficiency. This deficiency leads to a ***sensory neuropathy*** of ***peripheral nerves and dorsolateral columns***
- Etiology: lack of B12 intake, lack of intrinsic factor, or lack of B12-intrinsic factor complex absorption
    - Gastric urinary conduits may lead to intrinsic factor deficiency
    - Ileal urinary conduits may lead to decreased B12-intrinsic factor complex absorption
- Sx: paresthesias in hands/feet; decreased vibratory sensation in the lower extremities; urinary retention
- Lab: macrocytic (elevated MCV), normochromic (normal MCHC) anemia; hypersegmented neutrophils; megaloblasts; positive Schilling test
- Tx: B12 replacement; timed voiding ± CIC

HERPES ZOSTER (HZV) / HERPES SIMPLEX VIRUS (HSV)

- HZV (shingles) is an activation of dormant virus within the dorsal root ganglions
    - If a sacral dermatome is involved, acute urinary retention may develop
- ***Elsberg syndrome***: HSV-2 may result in acute urinary retention and

other neurologic findings due to acute sacral radiculomyelitis

  - Secondary to primary/acute infection with HSV-2 or activation of dormant HSV-2 in the sacral dorsal root ganglion
  - UDS: hypotonic/atonic bladder with sensation present (i.e. ***motor dysfunction***) – self limited; almost always resolves spontaneously within 12 weeks
- Tx: antivirals; timed voiding ± CIC while bladder dysfunction

ABDOMINOPERINEAL RESECTION (IATROGENIC)

- Injury to the Inferior hypogastric plexus (parasympathetic) leads to ***detrusor areflexia*** and ***erectile dysfunction***
- Injury to the pudendal nerve (somatic) leads to a ***fixed, contracted external sphincter***

| NEUROGENIC BLADDER TREATMENTS |

SPASTIC / DETRUSOR OVERACTIVITY

- Timed voiding
- Anti-cholinergic medications (see bladder dysfunction chapter)
- **Botulinum-A toxin**
  - Clostridium botulinum (anaerobic, gram-positive) neurotoxin that inhibits acetylcholine presynaptic exocytosis by cleaving SNAP25 proteins (a SNARE protein)
  - Effect lasts ~ 9 months, and requires repeat injections
  - ***OnabotulinumtoxinA*** (Botox®): FDA approved for:
    - Overactive bladder: 100 units over 20 injections sites
    - Neurogenic detrusor overactivity: 200 units over 30 injection sites
    - Side effects: UTI, urinary retention, dysuria
    - Aminoglycosides may potentiate the effects
  - **AbobotulinumtoxinA** (Dysport®): not FDA approved for bladder injection at the time of writing this chapter; however, several studies published regarding its usage.

Botulinum-A Toxin

Potency, biologic activity, and units are not interchangeable between different preparations of Botulinum-A toxin

- Clean intermittent catheterization (CIC), Foley catheter, or suprapubic tube
- Sphincterotomy with condom catheter (males only)
    - Creates irreversible, continuous urinary incontinence
- Rhizotomy
    - Sacral rhizotomy: converts hyperreflexia to areflexia
    - Selective dorsal Rhizotomy: maintain sphincter and sexual function
- Augmentation cystoplasty
    - Higher failure rate in idiopathic DO compared to neurogenic DO
    - Contraindications: Crohn's disease, irradiated bowel (relative)
- Urinary diversion

FLACCID / AREFLEXIC BLADDER

- Timed voiding
- ***Bethanechol*** (Urecholine®)
    - Parasympathomimetic (increases bladder contractions)
    - 25-50mg every 6-8 hours
- Clean intermittent catheterization (CIC), Foley catheter, or suprapubic tube
    - Patients with chronic suprapubic catheters require annual cystoscopy because of an increased risk for squamous cell carcinoma

CIC Frequency

CIC should be performed regularly and adjusted to maintain residual amounts < 400 mL

- TURP: reducing outlet resistance may decrease post-void residuals
- ***Sacral Neuromodulation*** (Interstim®)
    - *o* Exact mechanism of action is unknown
    - *o* Electrodes implanted into the S3 motor nerve root
        - * S3 implantation verified by anal bellows and great toe plantar flexion
        - * If S2 (wrong position): plantar flexion, foot rotation, buttock sensation
        - * If S4 (wrong position): anal bellows without leg/foot movement
    - *o* Indications: urinary retention (non-obstructive), urge incontinence (non-neurologic), urgency-frequency, chronic fecal incontinence
        - * Less effective if neurologic injury or congenitally maldeveloped nerves

CHAPTER 17: BLADDER DYSFUNCTION AND URINARY TRACT FISTULAS

| URINARY INCONTINENCE |

STRESS URINARY INCONTINENCE

- Urine leakage secondary to increased abdominal pressure (e.g. valsalva, cough)

ETIOLOGY

- **Urethral hypermobility** (type 1)
- **Intrinsic sphincter deficiency** (ISD; type 3)
    - Severe ISD is referred to as a stove pipe urethra

WORKUP

- Usually a clinical diagnosis via history and physical exam
- ***Marshall Test***: have a patient with a full bladder valsalva (e.g. cough or strain)
    - Urine leakage is a positive test for SUI
- ***Q-tip test***: insert a Q-tip into the urethra and have the patient valsalva
    - ≥ 30° movement is a positive test for urethral hypermobility
- Urodynamics is not necessary prior to surgery for routine SUI

TREATMENT

- Urethral hypermobility
  - Pelvic floor muscle training (Kegel exercises, biofeedback)
  - Transobturator midurethral sling
  - Burch urethropexy (periurethral tissue sutured to conjoined tendon or Cooper's ligament)
  - Marshall-Marchetti-Krantz (MMK; periurethral tissue sutured to pubic periosteum)
  - Success rates: midurethral sling ≈ Burch urethropexy > MMK
- Intrinsic sphincter deficiency
  - Pelvic floor muscle training
  - Urethral bulking – decreased durability, but less invasive than a sling
    - Agents: silicone microparticles, calcium hydroxyapatite, carbon-coated zirconium beads
    - If postoperative urinary retention, CIC with 10-14Fr catheter
  - Retropubic or transobturator midurethral sling

MIDURETHRAL SLINGS

- Overall midurethral sling success: ~ 75-85%
- Side effects
  - De novo overactive bladder / urgency (~ 5%)
  - Resolution of concurrent overactive bladder (up to 60%)
  - Urethral mesh erosion
  - Vaginal mesh extrusion
    - If asymptomatic, conservative treatment; may consider topical estrogen
    - If symptomatic or bothersome to sexual partner, transvaginal surgical removal
  - Dyspareunia
  - Bladder outlet obstruction / urinary retention (~ 5%)
    - Options: early return (within 2 weeks) to operating room to loosen/remove sling (preferable) vs. gentle dilation vs.

- Consider urinary dynamics studies

OVERFLOW URINARY INCONTINENCE

- Urine leakage secondary to a full bladder without detrusor contraction
- Tx: timed voiding, clean intermittent catheterization, treatment of outlet obstruction (e.g. TURP for BPH)
- ***Bethanechol*** (if not obstructed)
    - Muscarinic (parasympathetic) agonist resulting in increased detrusor tone (effectiveness is controversial)
    - Contraindications: asthma, peptic ulcer, hyperthyroidism, parkinsonism, vasomotor instability
    - Antidote: atropine

FUNCTIONAL URINARY INCONTINENCE

- Urine leakage secondary to mental or physical disability inhibiting toilet voiding (e.g. inability to ambulate, dementia, and depression)
- Tx: treat underlying conditions; timed voiding with assistance; absorbent pads
    - Behavioral modification: adequate lighting and assistance, remove items that may trip the patient, bedside toilet, etc.

CONTINUOUS URINARY INCONTINENCE

- Urine leakage at all times
- DDx: vesicovaginal fistula, ectopic ureter distal to the external urethral sphincter, stove pipe urethra
- Rule out overflow incontinence, which may be related to upper tract deterioration

INCONTINENCE AND PREGNANCY

Type	Nulliparous	Cesarean section	Vaginal delivery
Overall	10%	15%	20%
SUI	5%	7%	12%
Urge	2%	2%	2%
Mixed	3%	5%	6%

Approximate values (Rortveit, 2003)

| OVERACTIVE BLADDER (OAB) |

- Urinary urgency with at least one additional symptom, usually frequency and/or nocturia; may also have associated urge incontinence
    - o Women more commonly have associated incontinence
- ***OAB is a clinical diagnosis***
- ***Frequency***: usually > 8 voids/day
- Patients with OAB urinate frequently to avoid incontinence, while patients with interstitial cystitis urinate frequently to avoid pain.

Detrusor Overactivity

Urodynamic finding

Involuntary detrusor contractions

ETIOLOGY

- Unclear, but may be overexcited nerves, detrusor, and/or urothelial afferent input
    - o ***Alpha-delta fibers***: normal bladder afferent fibers (e.g. bladder fullness)

  - ***C-fibers***: pathologic bladder afferent fibers (e.g. chemical or thermal information)

WORKUP

- Good history and physical, including voiding and fluid-intake diaries
- Urinary analysis (rule out underlying UTI or microscopic hematuria)
  - ***20-30% of patients with bladder cancer present with irritative voiding symptoms, which may masquerade as OAB***
- Voiding / Lower Urinary Tract Symptom Questionnaires
- Post-void residual
- Consider urinary dynamic studies (UDS) if it is a complicated presentation or refractory to medical treatment
  - May be non-diagnostic

Detrusor Overactivity with Impaired Contractility

Most common diagnosis of incontinence found in frail, elderly women. Present with urge incontinence and elevated PVRs

TREATMENT

- Smoking cessation; decrease caffeine, alcohol, and dietary irritants; adjusting fluid intake
- Pelvic floor muscle training
  - **Biofeedback**
- Medications: see Urinary Urge Incontinence above for medication/ treatment details
  - **Anticholinergic** (Oxybutynin, Tolterodine, Trospium, Darifenacin, Solifenacin, Fesoterodine)
  - **Beta-3 Adrenergic Agonists** (Mirabegron)
  - **Botulinum Toxin** (OnabotulinumtoxinA)
  - **Tricyclic Antidepressants** (Imipramine)
  - **Estrogen topical vaginal cream**
- **Sacral Neuromodulation** (Interstim®)

| NOCTURIA |

- Awaking to void ≥ 1 at nighttime
- Categorized into 5 types of nocturia, which help guide treatment
- Will need 24 hour voiding diary to classify nocturia
  - o **Nocturnal Urine Volume**: urine volume during night time and 1st AM void
    - * Assuming a void prior bedtime, this accounts for volume produce throughout the night
  - o **Nocturnal Index**: nocturnal urine volume / functional bladder capacity (i.e. maximum voided volume for 24 hour period)
    - * If > 1, nighttime urine production exceeds bladder capacity, thus leading to nocturia
- ***Nocturnal Polyuria***: nocturnal urine volume > 35% of the 24-hour voided volume
  - o Etiology: fluid overload that is mobilized while recumbent (congestive heart failure (CHF), lower extremity venous stasis, diabetes mellitus), excessive fluid intake prior to bedtime, low nighttime ADH, sleep apnea (elevated ANP released from right atrial stretch)
  - o More common in older patients
  - o Treatment:
    - * Compression stockings, decreasing evening fluid intake
    - * Late afternoon / early evening diuretics and leg elevation
      - Diuresis begins relatively quickly, allowing urination of excess fluid prior nighttime
    - * ***Desmopressin*** (aka: DDAVP; vasopressin, ADH) at bedtime
      - Monitor BMP initially for hyponatremia
      - Side effects: nausea, vomiting, headache, lightheaded, worsening edema (particular CHF patients), hypertension (V1 receptor stimulation)
    - * **Sleep apnea**: CPAP/BiPAP

- ***Low Nocturnal Bladder Capacity***: decreased bladder capacity at night time (voided amounts never amount to maximal voided volume over 24 hours)
    - o Etiology: bladder outlet obstruction, neurogenic bladder, cystitis, bladder calculi, neoplasia, OAB
    - o More common in younger patients
    - o Dx: cystoscopy, urinary dynamic studies; nocturnal index < 1
    - o Treatment: treat underlying cause; decrease evening fluid intake; sacral neuromodulation
        - * NOTE: alpha blockers and 5-alpha reductase inhibitors are not very effective at treating nocturia
- ***Mixed Polyuria (Nocturnal Polyuria and Low Bladder Capacity)***
    - o Treatment: treat predominant aspect first
- ***Diminished Global Bladder Capacity***: small volume voids at all times, day or night
    - o Etiology is similar to low nocturnal bladder capacity, except not just at nighttime
- ***Global Polyuria***: 24 hour urine > 40cc/kg
    - o Etiology:
        - * Diabetes insipidus: central (low ADH), nephrogenic (decreased ADH receptors/response to ADH), or gestational (placental vasopressinase decreases maternal ADH)
        - * Primary polydipsia: dipsogenic diabetes insipidus (hypothalamic injury to thirst center) vs. psychogenic
        - * Diabetes mellitus: osmotic diuresis (hyperglycemia)
    - o Treatment:
        - * **Central diabetes insipidus**: Desmopressin
        - * **Gestational diabetes insipidus**: Desmopressin
        - * **Nephrogenic diabetes insipidus**: Thiazide diuretic (paradoxical effect)
        - * **Dipsogenic diabetes insipidus**: No treatment; some reports of low dose Desmopressin
        - * **Diabetes mellitus**: better glucose control

        * **Psychogenic polydipsia**: Fluid restriction, correct hyponatremia, behavioral and psychological treatment

| PELVIC ORGAN PROLAPSE (POP) |

- ***POP***: anterior vaginal wall (cystocele), posterior vaginal wall (rectocele), vaginal apex / cervix (uterine prolapse), or vaginal cuff (enterocele) descent
    - May have concurrent urinary incontinence, occult urinary incontinence, voiding symptoms, and outlet obstruction
    - Treatment is only indicated for symptomatic POP

VAGINAL SUPPORT LEVELS

- ***Level 1: uterosacral and cardinal ligament***
    - Cervical / upper vaginal support
    - Loss of support results in vaginal / uterine prolapse
    - Tx: uterosacral ligament suspension; sacrospinous fixation
        * May have occult cystocele

Sacrospinous Ligament Fixation

Nonabsorbable sutures are placed through the ligament, and not around it to avoid a pudendal neurovascular bundle injury

- ***Level 2: arcus tendineus fascia pelvis***
    - Paravaginal support
    - Loss of support results in cystocele
- ***Level 3: perineal body, membrane, and muscles***
    - Urethral and distal vaginal support
    - Loss of support results in urethral hypermobility (SUI) and/or rectocele

- ***Endopelvic fascia***: supports vaginal walls, particularly apical support, which when lax or defective, allows peritoneal herniation
    - Loss of support results in an enterocele
- ***Rectovaginal fascia***: supports posterior vaginal and anterior rectal walls
    - Midline posterior defect results in a rectocele

CYSTOURETHROCELE

- ***Paravaginal (lateral) defect***
    - Pubocervical fascia separates from the arcus tendineus fascia pelvis (i.e. lateral loss of support)
    - Associated with SUI
    - Tx: ***re-suspend the pubocervical fascia*** (vaginal sidewall) ***to the arcus tendineus fascia pelvis*** (pelvic sidewall)
- ***Transverse defect***
    - Pubocervical fascia separates from pericervical ring (i.e. apical loss of support)
    - Tx: ***abdominal sacrocolpopexy***
- ***Midline (central) defect***
    - Pubocervical fascia separates in the midline; nearly always concurrent with a paravaginal defect
    - Associated with SUI
    - Tx: ***anterior colporrhaphy*** (midline pubocervical fascia plication)
- ***Distal defect (urethrocele)***
    - Periurethral attachments separate from the urogenital diaphragm with loss of pubic symphysis attachment
    - Associated with SUI

PELVIC ORGAN PROLAPSE QUANTIFICATION (POP-Q)*

Stage	Description
0	No prolapse
1	Distal portion of prolapse is > 1cm above the hymen
2	Distal portion of prolapse is 1 cm above or below the hymen
3	Distal portion of prolapse is > 1cm below the hymen, but not total prolapse
4	Total vaginal prolapse

** Measuring point is hymenal ring while patient is in dorsal lithotomy during valsalva. Proximal to the hymen is a positive value, and distal is a negative value.*

POP-Q MEASUREMENTS

Measurements	Nomenclature	Clinically Significance if Positive Values
Anterior	Aa, Ba	Cystocele
Posterior	Ap, Bp	Rectocele
Cervix/Cuff, pouch of Douglass	C, D	Enterocele, Uterine prolapse

OTHER TREATMENT OPTIONS

- **Vaginal Pessary**: synthetic object in various shapes placed intravaginally that reduces the POP
    - o Good option for patients that lack the desire for surgery or are not surgical candidates
- **Colpocleisis**: surgical closure of the vagina
    - o Elderly females that are no longer sexually active with symptomatic POP
- **Mesh reconstruction**: FDA warning for exposure (~10%), contraction, dyspareunia (up to 15%; pain improves in time), pelvic pain, erosion

  - Mesh has decreased failure rates compared to anterior suture repairs (4-8% vs. 30-60%)
  - ***Exposure***: if asymptomatic and not sexually active, consider monitoring the exposure.
    - Consider vaginal estrogen cream for 3 months, if vaginal atrophy present.
    - If symptomatic, small (< 0.5cm), and visible on exam, trim the exposure in the office.
    - If symptomatic and larger, excise the exposure in the operating room.

| RADIATION CYSTITIS |

- Inflammatory reaction of the bladder secondary to radiation therapy that may occur in months to several years (up to 20 years) after radiation exposure
- Pathology: ***hypovascular, hypocellular, hypoxia***
  - Free oxygen radicals causes lipid peroxidation
  - Genetic damage occurs directly by radiation, and indirectly by free oxygen radicals
  - Smooth muscle is replaced by fibroblasts
  - Ischemia ultimately leads to fibrosis
- Sx: irritative urinary symptoms, hematuria, urgency, frequency, contracted bladder
  - Late appearing symptoms (6 months to 20 years) occur secondary to latent vascular endothelial cell damage resulting in ***obliterative endarteritis***, thus most commonly presenting with ***hematuria***
- Dx: urinary analysis, urine cytology, cystoscopy + biopsy, upper tract imaging
- Tx: ***Acute radiation cystitis***: usually self-limiting and resolves spontaneously within 3 months, so treat with anticholinergics and Phenazopyridine

- ***Late radiation cystitis*** (5-10% incidence) treatments:
    - Catheter irrigation – normal saline
    - Intravesical instillation
        - **Alum 1%** (aluminum with potassium sulfate or ammonium sulfate); protein precipitation
        - **Placental extract**
        - **Formalin**: 4% for 10-30 minutes; may result in bladder cripple; must be performed under anesthesia and not have vesicoureteral reflux
    - Oral / parenteral medications
        - **Conjugated estrogens**: stabilizes vascular fragility; contraindications – hepatic disease, clotting disorder, endometrial/breast cancer
        - **WF10 (tetrachlorodecaoxide):** activates macrophage tissue repair
        - **Pentosan polysulfate**: synthetic glycosaminoglycan layer
    - Cystoscopy with fulguration
    - Hyperbaric oxygen therapy: successful ~ 80% of patients
        - May be used if refractory to other treatments
        - If initially controlled, may be utilized for possible cure
    - Surgical intervention
        - **Percutaneous nephrostomy**: urinary diversion to limit urothelial exposure to urokinase
        - **Internal iliac artery embolization**: reserved for intractable hematuria
        - **Urinary diversion +/- cystectomy**: last resort; lack of cystectomy has high risk of pyocystis, hemorrhage, pain, and neoplastic transformation

  - Mesh has decreased failure rates compared to anterior suture repairs (4-8% vs. 30-60%)
  - ***Exposure***: if asymptomatic and not sexually active, consider monitoring the exposure.
    - Consider vaginal estrogen cream for 3 months, if vaginal atrophy present.
    - If symptomatic, small (< 0.5cm), and visible on exam, trim the exposure in the office.
    - If symptomatic and larger, excise the exposure in the operating room.

| RADIATION CYSTITIS |

- Inflammatory reaction of the bladder secondary to radiation therapy that may occur in months to several years (up to 20 years) after radiation exposure
- Pathology: ***hypovascular, hypocellular, hypoxia***
  - Free oxygen radicals causes lipid peroxidation
  - Genetic damage occurs directly by radiation, and indirectly by free oxygen radicals
  - Smooth muscle is replaced by fibroblasts
  - Ischemia ultimately leads to fibrosis
- Sx: irritative urinary symptoms, hematuria, urgency, frequency, contracted bladder
  - Late appearing symptoms (6 months to 20 years) occur secondary to latent vascular endothelial cell damage resulting in ***obliterative endarteritis***, thus most commonly presenting with ***hematuria***
- Dx: urinary analysis, urine cytology, cystoscopy + biopsy, upper tract imaging
- Tx: ***Acute radiation cystitis***: usually self-limiting and resolves spontaneously within 3 months, so treat with anticholinergics and Phenazopyridine

- ***Late radiation cystitis*** (5-10% incidence) treatments:
    - Catheter irrigation – normal saline
    - Intravesical instillation
        - **Alum 1%** (aluminum with potassium sulfate or ammonium sulfate); protein precipitation
        - **Placental extract**
        - **Formalin**: 4% for 10-30 minutes; may result in bladder cripple; must be performed under anesthesia and not have vesicoureteral reflux
    - Oral / parenteral medications
        - **Conjugated estrogens**: stabilizes vascular fragility; contraindications – hepatic disease, clotting disorder, endometrial/breast cancer
        - **WF10 (tetrachlorodecaoxide):** activates macrophage tissue repair
        - **Pentosan polysulfate**: synthetic glycosaminoglycan layer
    - Cystoscopy with fulguration
    - Hyperbaric oxygen therapy: successful ~ 80% of patients
        - May be used if refractory to other treatments
        - If initially controlled, may be utilized for possible cure
    - Surgical intervention
        - **Percutaneous nephrostomy**: urinary diversion to limit urothelial exposure to urokinase
        - **Internal iliac artery embolization**: reserved for intractable hematuria
        - **Urinary diversion +/- cystectomy**: last resort; lack of cystectomy has high risk of pyocystis, hemorrhage, pain, and neoplastic transformation

| VESICAL FISTULA |

ENTEROVESICAL / COLOVESICAL FISTULA

- Communication between the small bowel or colon and bladder
    - o Dome (60%), posterior wall (30%), trigone (10%)
- Etiology: diverticulitis (60%; colon), colorectal malignancy (20%; colon), Crohn's disease (10%; ileum), trauma, history of radiation therapy, appendicitis
- Sx: ***Pneumaturia***, fecaluria, recurrent UTI, diarrhea (urine within the rectum), frequency, dysuria, hematuria
- Dx: cystoscopy with biopsy, CT cystogram, CT abdomen/pelvis with oral contrast, barium enema x-ray (colon), colonoscopy with biopsy, small bowel follow through, urine culture
    - o ***Bourne test***: after a barium enema study, centrifuge the 1st voided urine and x-ray the sediment. If radio-opaque material present = enterovesical fistula
- Tx: fistula resection, colonic / ileal resection with primary anastomosis, bladder closure, Foley catheter for 10-14 days

Gouverneur's Syndrome

Classic enterovesical fistula presentation:

Suprapubic pain, frequency, dysuria, tenesmus

VESICOVAGINAL FISTULA

- Communication between the bladder and vagina
- Etiology: injury during pelvic surgery (> 75%), history of radiation, malignancy, obstetrical trauma, pelvic inflammatory disorder
- Sx: continuous urinary incontinence, vaginal discharge, recurrent UTI, hematuria
- DDx: ureterovaginal fistula
    - o ***Double dye test*** – with a tampon in the vagina, the patient

takes Phenazopyridine orally, and then methylene blue stained water is injected into the bladder via a catheter.

- * If the tampon is ***orange***: ***ureterovaginal fistula***
- * If the tampon is ***blue***: ***vesicovaginal fistula***

- o Cystoscopy +/- retrograde pyelogram
- o Vaginal speculum exam
- o VCUG

Vesical Fistulas

All vesical fistulas require biopsy during cystoscopy to rule out malignancy

- Tx: if acute, small (< 3-5mm) and secondary to surgical procedure, may consider conservative treatment with Foley catheter and anticholinergics for 2-4 weeks, which may result in spontaneous closure
  - o Transvaginal, laparoscopic, or open surgical repair
    - * Interpositional flaps reduce fistula recurrence

INTERPOSITIONAL FLAPS FOR FISTULA REPAIRS

Flap	Arterial Sacrifice	Arterial Supply	Surgical Approach
Omental	Left gastroepiploic	Right gastroepiploic*	Transabdominal
Peritoneal	---	---	Proximal fistula during vaginal approach
Martius	External pudendal	Posterior labial (internal pudendal)	Distal fistula during vaginal approach

** Right gastroepiploic is preferred because it may be mobilized further into the pelvis*

| VESICAL FISTULA |

ENTEROVESICAL / COLOVESICAL FISTULA

- Communication between the small bowel or colon and bladder
  - Dome (60%), posterior wall (30%), trigone (10%)
- Etiology: diverticulitis (60%; colon), colorectal malignancy (20%; colon), Crohn's disease (10%; ileum), trauma, history of radiation therapy, appendicitis
- Sx: ***Pneumaturia***, fecaluria, recurrent UTI, diarrhea (urine within the rectum), frequency, dysuria, hematuria
- Dx: cystoscopy with biopsy, CT cystogram, CT abdomen/pelvis with oral contrast, barium enema x-ray (colon), colonoscopy with biopsy, small bowel follow through, urine culture
  - ***Bourne test***: after a barium enema study, centrifuge the 1st voided urine and x-ray the sediment. If radio-opaque material present = enterovesical fistula
- Tx: fistula resection, colonic / ileal resection with primary anastomosis, bladder closure, Foley catheter for 10-14 days

Gouverneur's Syndrome

Classic enterovesical fistula presentation:

Suprapubic pain, frequency, dysuria, tenesmus

VESICOVAGINAL FISTULA

- Communication between the bladder and vagina
- Etiology: injury during pelvic surgery (> 75%), history of radiation, malignancy, obstetrical trauma, pelvic inflammatory disorder
- Sx: continuous urinary incontinence, vaginal discharge, recurrent UTI, hematuria
- DDx: ureterovaginal fistula
  - ***Double dye test*** – with a tampon in the vagina, the patient

takes Phenazopyridine orally, and then methylene blue stained water is injected into the bladder via a catheter.

- If the tampon is ***orange***: ***ureterovaginal fistula***
- If the tampon is ***blue***: ***vesicovaginal fistula***

- Cystoscopy +/- retrograde pyelogram
- Vaginal speculum exam
- VCUG

Vesical Fistulas

All vesical fistulas require biopsy during cystoscopy to rule out malignancy

- Tx: if acute, small (< 3-5mm) and secondary to surgical procedure, may consider conservative treatment with Foley catheter and anticholinergics for 2-4 weeks, which may result in spontaneous closure
  - Transvaginal, laparoscopic, or open surgical repair
    - Interpositional flaps reduce fistula recurrence

INTERPOSITIONAL FLAPS FOR FISTULA REPAIRS

Flap	Arterial Sacrifice	Arterial Supply	Surgical Approach
Omental	Left gastroepiploic	Right gastroepiploic*	Transabdominal
Peritoneal	---	---	Proximal fistula during vaginal approach
Martius	External pudendal	Posterior labial (internal pudendal)	Distal fistula during vaginal approach

** Right gastroepiploic is preferred because it may be mobilized further into the pelvis*

URETEROVAGINAL FISTULA

- Connection between a ureter and the vagina
- Etiology: hysterectomy, vascular surgery, malignancy, history of radiation, pelvic trauma, infection
- Sx: continuous urinary incontinence with a normal voiding pattern (particularly a few weeks after pelvic surgery), abdominal/flank pain, nausea
  - Ureteral fistula results in the continuous incontinence, while the contralateral ureter results in normal bladder filling and voiding
- Dx: double dye test, cystoscopy with retrograde pyelogram, IVP, CT urogram
- Tx: attempt conservative treatment with ureteral stent placement for 4-6 weeks
  - If unable to place stent or persistent fistula after stent placement, proceed with ureteroneocystostomy

VESICOUTERINE FISTULA (*YOUSSEF SYNDROME*)

- Connection between the bladder and uterus; rare
- Etiology: caesarean section (most common), foreign body, trauma, bladder injury
- Sx: menouria, cyclic hematuria, amenorrhea, urinary incontinence with previous caesarean section
- Dx: cystoscopy, cystogram, hysterosalpingogram, urine cytology, MRI
- Tx: treatment depends on fertility desires
  - If no longer desires fertility: hysterectomy with cystorrhaphy
  - If desires future fertility: excise fistula, repair uterus/bladder, and place an interpositional flap

CHAPTER 18: URINARY DYNAMIC STUDIES (UDS)

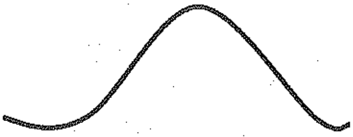
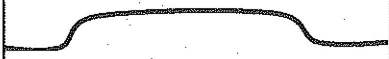
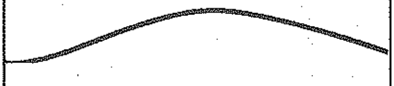
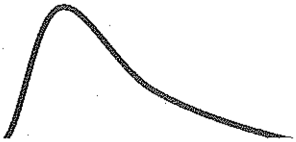
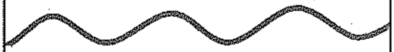
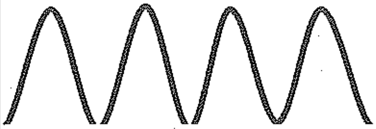
INDICATIONS

- Mixed urinary incontinence
- Refractory overactive bladder
- Refractory urinary retention
- Suspected neurogenic bladder / neurologic condition
- Male stress urinary incontinence
- Female stress urinary incontinence not seen on exam
- Cystocele (determine if underlying stress urinary incontinence)
- Voiding difficulties with previous pelvic / genitourinary surgery

| UROFLOWMETRY |

- Patient voids into a specialized container with computerized monitoring to calculate urine flow over time, and determines several values:
    - Qmax (maximum flow rate, ml/second)
    - Qavg (average flow rate, ml/second)
    - Time to maximum flow
    - Voiding time
    - Check post-void residual to determine emptying ability

UROFLOWMETRY DIAGNOSTIC FINDINGS

Diagnosis	Uroflometry	Pattern
Normal		Bell Curve
Urethral Stricture		Plateau
Bladder Outlet Obstruction		Prolonged bell curve Low Qmax
Detrusor Overactivity		High Qmax immediately, then tapers
Detrusor Hypocontractility		Wavy flow Low Qmax
Interrupted Flow (Abdominal voiding; Shy bladder)		Wavy flow High/normal Qmax

- ***Must void at least 150 cc to have a valid study*** (very large volumes may also invalidate the study)
- Indicates a voiding problem, but can not reliably differentiate between obstruction and hypotonicity

UROFLOW MAXIMUM FLOW RATE NORMAL RANGES

Gender / Age	Uroflow Qmax (ml/sec)
Males < 40 years old	> 25
Males 40-60 years old	15-25
Males > 60 years old	> 15
Females	> 15

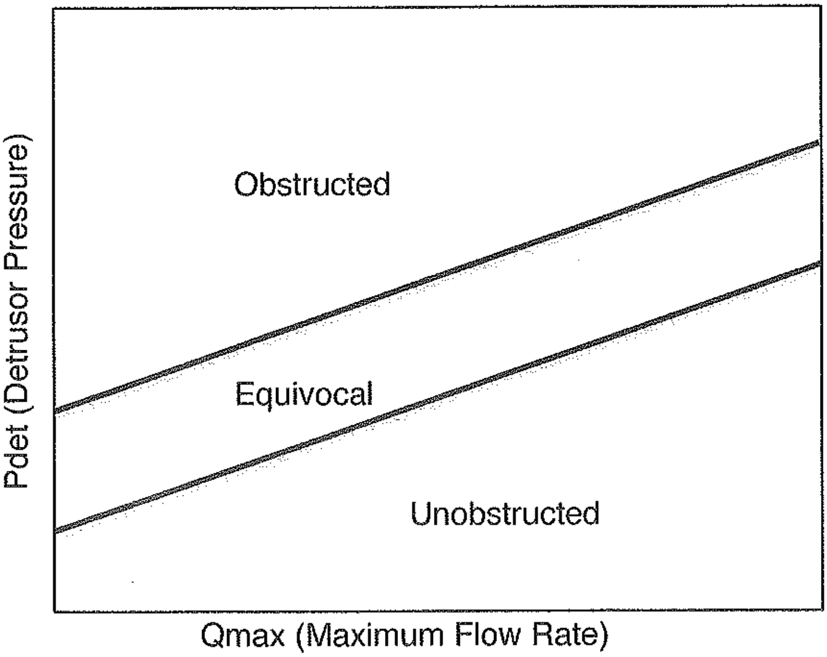
| CYSTOMETRY |

- Patient has a small (6-8 French), specialized Foley catheter inserted, then measurements are taken during filling and voiding phases
- The Foley measures the **intravesical pressure (Pves)** and allows filling
    - o Adult fill rate: ***~ 50 mL/minute***
    - o Pediatric fill rate: ***bladder capacity / 10; or weight in kilograms / 4***
        - * Pediatric bladder capacity (mL)
            - If < 1 year of age = 7 x weight (in kilograms)
            - If > 1 year of age = (age + 2) x 30
- Rectal or vaginal catheter to measure **abdominal pressure (Pabd)**
    - o Start all cystometrograms with a cough to test the setup

Pdet = Pves – Pabd

- **Detrusor pressure (Pdet) = Pves – Pabd**
    - o Pdet is a calculated value, not a measured value
    - o Normally Pdet has little change during filling, as normal bladders are very compliant

  - ***Detrusor pressure is a function of outlet resistance.*** (e.g. an enlarged prostate with obstruction will lead to increased detrusor voiding pressure)
  - Pdet and Qmax may be used in nomograms to determine if bladder obstruction, equivocal, or unobstructed



- **External sphincter EMG** via skin patch or needle
- **Urethral pressure profile**: measured by the urethral catheter
  - ***Mean Urethral Closure Pressure (MUCP)*** normally < 20 cmH20
- **Fluoroscopy (video urodynamics)**: useful when neurologic conditions, female obstructed voiding pattern, young male obstructed voiding pattern, diverticulum, fistula, posterior urethral valves

FILLING PHASE

- **Capacity**
  - Normal bladder capacity is 400-600 mL
  - **MCC (maximum cystometric capacity)** = 400-600 mL

- **Compliance** = ($\Delta V / \Delta P$)
    - Change in bladder volume ÷ change in detrusor pressure
    - ***Normal: > 30 – 60 mL / cmH2O***
    - Poor compliance: consistently increasing Pves or Pdet during filling without change in abdominal pressure and no leaking
        - Graphically seen as 30-45 degree Pdet slope
- **Continence**
    - ***Stress***
        - Graphically seen as increases in Pabd with urine leakage
    - ***Detrusor Overactivity (DO) ± leak***: this is a urodynamic finding (if clinical finding without UDS, then considered overactive bladder)
        - Graphically seen as increases in Pdet during filling (wavy line)
        - ***Idiopathic*** vs. ***Neurogenic*** (underlying neurologic disorder)
            - Dry vs. Wet = if leak present during bladder contraction
            - 50% of urge incontinence is not reproducible on UDS
        - Radiographically (video-UDS): ***spinning top urethra*** (particularly in pediatrics)
- **Sensation / Desire**
    - Note 1st sensation/desire (normally 50-150 mL)
    - Diabetic cystopathy has decreased 1st sensation
- **Valsalva (Abdominal) Leak Point Pressure (VLPP or ALPP)**
    - Patient performs valsalva to determine if leak, and at what pressure
    - Normal = no leak
    - Stress urinary incontinence = leak

VLPP PRESSURES, DIAGNOSIS, AND TREATMENT

VLPP (cm of water)	Diagnosis	Treatment
> 90	Urethral hypermobility	Transobturator midurethral sling
60 – 90	Gray zone	
< 60	Intrinsic sphincter deficiency	Urethral bulking agent, pubovaginal midurethral sling

- **Detrusor Leak Point Pressure (DLPP)**
    - Urinary leakage secondary to increased detrusor pressure without a bladder contraction, nor an increase in abdominal pressure ("pop-off mechanism" to protect the bladder and upper tracts)
    - ***Normal is < 40 cmH20***
        - Ureteral peristalsis pressure is 35 cmH2O, so greater pressures in the bladder are transmitted to the upper tracts, and may cause renal injury
    - Commonly elevated in spinal cord injury, spinal bifida
        - Tx: CIC; CIC + anticholinergic; vesicostomy (infants); OnabotulinumtoxinA vesical injections; bladder augmentation
            - CIC: chronic bacteriuria (if asymptomatic, do not treat)
            - Vesicostomy: place at dome to reduce bladder prolapse

ALPP vs. DLPP

ALPP: abdominal pressure increased with valsalva (e.g. cough) resulting in stress urinary incontinence

DLPP: urinary leakage without bladder contractions nor an increase in abdominal pressure, resulting in overflow incontinence

- **Bethanechol Supersensitivity Test**
  - Administer subcutaneous bethanechol and measure detrusor pressure
    - Positive: > 15 cmH2O rise in detrusor pressure during filling
  - Increased sensitivity to acetylcholine is seen in denervated / neurogenic bladders

VOIDING PHASE (PRESSURE-FLOW STUDIES)

- **Contractility**
  - Detrusor ability to contract during voiding
  - Measured by Qmax and Pdet combination

DETRUSOR CONTRACTILITY

Qmax (mL/sec)	Pdet (cmH2O)	Diagnosis
High	Low	Normal
Low	High	Male bladder outlet obstruction
Low	Low	Neurogenic bladder / Straining
< 12	≥ 25	Female bladder outlet obstruction

- **Communication**
  - Determine if detrusor sphincter synergy vs. dyssynergia
    - EMG normally (synergy) increases during filling and is minimal during voiding
- **Completeness**
  - Check post-void residual to determine if urinary retention

CYSTOMETROGRAM SUMMARY

Filling Phase		***Voiding Phase***	
Capacity	MCC = 400-600 mL	Completeness	PVR < 50-100 mL
Compliance	> 30-60 mL/cmH2O	Contractility	Qmax > 20 mL/sec Pdet < 20 cmH20
Continence	SUI DO – wet / dry	Communication	Synergy Dyssynergy
1st Sensation	50-150 mL		

MCC = maximum cystometric capacity, SUI = stress urinary incontinence, DO = detrusor overactivity, PVR = post-void residual

CHAPTER 19: BENIGN PROSTATIC HYPERPLASIA (BPH)

ETIOLOGY

- Multiple theories; however, the exact etiology is unknown
- ***Androgens***: necessity for BPH to occur, but not etiology
    - Potency: dihydrotestosterone (DHT) > testosterone
        - DHT has greater androgen receptor affinity
        - Usually normal levels of DHT and testosterone are seen in BPH
    - ***5-alpha-reductase***: converts testosterone to DHT
        - Type 1: extraprostatic predominant (unclear clinical significance)
        - Type 2: prostatic predominant; particularly stromal cells
    - DHT or testosterone bind the androgen receptor, which leads to gene transcription within the nucleus and ultimately protein synthesis
        - If androgens are blocked or withdrawn, these genes are no longer transcribed and apoptosis genes are activated

Prostatic Androgens – "90/10 rule"

Origin: testicular 90% and adrenals 10%

Form: dihydrotestosterone 90% and testosterone 10%

- ***Estrogen***: unclear relationship
- ***Growth Factors***: in conjunction with DHT, may lead to hyperplasia
  - o Hyperplasia: Fibroblastic growth factor (FGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), epidermal growth factor (EGF)
    - * Keratinocyte growth factor (KGF; aka ***FGF-7***) may be key
  - o Apoptosis: transforming growth factor-beta (TGF-β)
- ***Hypoxia***: leads to increased hypoxia inducing factor-1 (HIF-1; as it does in renal tumors) and subsequent FGF stromal production
- ***Inflammation***: increased cytokines may lead to BPH
- ***Genetics***: younger men and/or greater prostatic volume likely have a underlying genetic predisposition for BPH; may be autosomal dominant
- ***Prolactin***: unclear relationship
- ***Metabolic syndrome***: associated with BPH/LUTS
  - o Increased prostatic volume, hyperplasia, adenoma size
- ***Alcohol intake***: protective against BPH (decreased testosterone levels may be etiology)
- ***Smoking***: unclear; likely weak relationship if present
- ***HTN***: increased alpha-adrenergic stimulation theoretically increases prostatic smooth muscle tone, but unproven

EPIDEMIOLOGY

- Occurs in almost no one < 30 years old, and almost everyone > 90 years old; its incidence increases in a near linear fashion from 30-90 years of age.

HISTOLOGY

- Periurethral hyperplastic nodules composed of stromal and epithelial cells
- BPH is a histologic diagnosis (enlarged prostate is a clinical diagnosis)
- ***Basal cells are present***
  - o ***HMWK*** or ***34βE12*** (High molecular weight keratin) ***– positive***
  - o ***P63 – positive***

  - ***AMACR*** (α-methylacyl-CoA racemase) – ***negative***
- ***Stroma***: smooth muscle and extracellular matrix
- ***Epithelial cells***: prostatic glandular cells
  - ***Corpora amylacea***: calcified prostatic secretions located between the transitional and peripheral zones
    - May be confused with prostatic abscess

PATHOPHYSIOLOGY

- ***Transitional zone*** is the key site for BPH, and adenoma development
  - This periurethral hyperplasia leads to bladder outlet obstruction, increased voiding pressures, and subsequent deleterious effects
- The prostatic capsule contains the hyperplasia; however, this leads to increased urethral lumen pressure, thus higher voiding pressures
- A considerable amount of ***prostatic smooth muscle*** is present, which responds to α-1 adrenergic receptors, particularly ***α-1a receptors***. Sympathetic stimulation leads to increased urethral pressures.
  - Example: post-surgical patients are in a hyperdynamic state, which may ultimately lead to post-operative urinary retention in patients without BPH.
- Correlated with erectile dysfunction; unclear if secondary to BPH or other factors (e.g. aging, diabetes) associated with BPH

LOWER URINARY TRACT SYMPTOMS (LUTS)

- ***Prostatic enlargement / volume*** – DRE, TRUS, or MRI
  - DRE: notoriously underestimates true volume
  - TRUS: prolate ellipsoid formula calculates prostate volume (length x height x width)(π / 6) or (length x height x width x 0.524)

Correlation of Prostate / Bladder Outlet Obstruction

Prostatic volume ≠ degree of symptoms ≠ degree of obstruction

- ***Symptoms*** – IPSS (international prostate symptom score)
  - Symptomatic assessment: incomplete emptying, frequency, intermittency, urgency, weak stream, straining, nocturia
    - Mild: 0-7 points
    - Moderate: 8-19 points
    - Severe: 20-35 points
  - Quality of life assessment: 0 (Delighted) - 6 (Terrible)
  - Rule out ***polyuria*** (symptoms: frequency, urgency) and ***nocturnal polyuria*** (symptom: nocturia)
    - Polyuria: > 3L per 24 hours of urine output
    - Nocturnal polyuria: > 33% of 24 hour urine output at nighttime
- ***Bladder outlet obstruction*** – uroflow, UDS, cystoscopy, post-void residual

UROFLOW MAXIMUM FLOW RATE*

Age (years)	Uroflow Qmax (mL/sec)
< 40 (normal)	> 25
40-60 (normal)	15-25
> 60 (normal)	> 15
> 60 (intermediate)	10-15
> 60 (obstructed)	< 10

** Must void > 150 mL to have a valid study*

BLADDER PATHOPHYSIOLOGY RELATED TO BPH

- ***Detrusor hypertrophy***: secondary to increased intravesical pressure
- ***Decreased compliance***: secondary to detrusor hypertrophy with collagen type 1 and 3 deposition
- ***Detrusor instability*** results in overactive bladder +/- incontinence
- ***Bladder trabeculation***: detrusor collagen deposition
- ***Diverticulum*** and ***cellules***: related to elevated voiding pressures
- ***Bladder calculi***: increased risk; however, still relatively low risk (~3%)
    - Screen if hematuria, recurrent UTI, stuttering urination
    - Usually terminal hematuria
- ***Upper tract injury***: usually identified by bilateral hydronephrosis, which if untreated, will lead to renal insufficiency
- ***Hematuria***: prostatic varices vs. bladder distention
- ***Acute urinary retention***: increasing PSA is correlated with an increased incidence of retention
- ***UTI***

BLADDER CHANGES SECONDARY TO BPH

Phase	Pathophysiology	Symptoms
Voiding	Decreased contractility	Hesitancy, intermittency, weak stream
Storage*	Decreased compliance, detrusor instability	Urgency, frequency

** Post-surgical removal of prostatic obstruction results in 1/3 of patients continuing with storage-type symptoms. May benefit from anticholinergics in absence of elevated post-void residuals.*

| MEDICATIONS |

5-ALPHA REDUCTASE INHIBITORS

- Inhibit conversion of testosterone to DHT
- ***Finasteride***
    - Half-life: 6-8 hours; bioavailability ~ 60%
    - Inhibits ***5α-reductase type 2***
    - Serum DHT reduced by 70%
- ***Dutasteride***
    - Half-life: 5 weeks; bioavailability ~ 60%
    - Inhibits ***5α-reductase type 1 and 2***
    - Serum DHT reduced by 90-95%
- Overall class effect: decreased prostate volume, risk of acute urinary retention, and BPH-related surgery; increased urine flow rate
- Side effects: decreased libido, impotence, breast tenderness, gynecomastia
    - ***PCPT trial***: decreases prostate cancer by ~ 25%; however, may slightly increase high grade prostate cancer (Gleason 8-10)
    - Moderate increase in LH, testosterone, and thyroid stimulating hormone (TSH)
    - No effect on lipid profile nor bone mineral density

5α-Reductase Inhibitors and PSA

Anticipate a near 50% reduction of PSA with finasteride (1mg and 5mg doses) and dutasteride

- ***PLESS trial***: finasteride vs. placebo showed an 18% decrease and 14% increase in prostate volume, respectively.
    - Volume nadir was reached at 1 year and sustained
    - ~ 50% decreased risk for acute urinary retention and surgical intervention
- ***Expect the PSA to decrease ~ 50%***
    - This effectively increases PSA sensitivity; therefore, any increases in PSA while on these meds necessitates a TRUS with prostate biopsy
    - This includes both finasteride doses for alopecia and BPH

ALPHA-1 BLOCKERS

- Androgen blockade results in prostatic smooth muscle (***α1-A***) and bladder neck relaxation (***α1-D***)
- Silodosin, Tamsulosin, Alfuzosin, Terazosin, Doxazosin, Prazosin
    - Silodosin: greatest affinity to alpha-1a receptors
    - Tamsulosin: relatively selective to alpha-1a receptors
- Side effects: retrograde ejaculation or decreased seminal ejaculate; rhinitis; intraoperative floppy iris syndrome (IFIS); dizziness; orthostatic hypotension
    - ***IFIS***: If patient has cataract surgery planned, await until completed prior to starting an alpha blocker
    - Separate timing of alpha blockers and phosphodiesterase type 5 inhibitors (e.g. sildenafil) to avoid potential hypotension
    - Alfuzosin, doxazosin, terazosin: much less retrograde ejaculation and little to no anejaculation as compared to tamsulosin and silodosin (the alpha-1a receptor affinity increases ejaculatory dysfunction)

α-Reductase Inhibitors vs. α-1 Blockers

α-Reductase Inhibitors: decreases risk for surgery; alters BPH disease process

α-1 Blocker: delays need for surgery; does not alter disease process

COMBINATION THERAPY (5-ALPHA REDUCTASE INHIBITORS + ALPHA BLOCKER)

- ***MTOPS trial***: combination doxazosin and finasteride significantly decreased the risk of overall BPH clinical progression (i.e. AUA symptom score increase of 4 points, acute urinary retention, renal insufficiency, or recurrent UTI)
  - Doxazosin alone: 39% risk reduction
  - Finasteride alone: 34% risk reduction
  - Combination therapy: 66% risk reduction
    - Also decreased risk of surgical intervention (finasteride effect)
- ***CombAT trial***: combination dutasteride and tamsulosin significantly decreased BPH symptoms
  - Greatest benefit is seen in patients with ***prostate volume ≥ 40 mL***
  - Acute urinary retention occurred more often with tamsulosin-alone than dutasteride-alone or combination therapy
- **SMART trial**: combination dutasteride and tamsulosin, and then subsequent removal of tamsulosin
  - 24 months of combination therapy resulted in rapid symptom improvement with a majority of patients maintaining symptom relief once stopping tamsulosin at 24 months. Note: Patients with severe symptoms (IPSS ≥ 20) did better with combination therapy.

PHOSPHODIESTERASE-5 INHIBITORS

- Tadalafil daily results in prostate smooth muscle relaxation
    - o ***Contraindication: concomitant nitrates***
- Decrease in IPPS score by 6.5 points on average (3.8 with placebo); maximum urine flow did not significantly increase.

ANTICHOLINERGICS

- See Bladder Dysfunction Chapter for details on anticholinergics
- Overactive bladder is a common result of bladder outlet obstruction / BPH, and is significantly improved with anticholinergics
    - o No increased risk of acute urinary retention in appropriate selected patients

MISCELLANEOUS

- ***Saw Palmetto (serenoa repens)***: ineffective treatment of BPH with LUTS
    - o **STEP trial**: regular dose saw palmetto is ineffective
    - o **CAMUS trial**: high dose saw palmetto is ineffective
- ***African plum tree (Pygeum africanum)***: may be effective treatment of BPH with LUTS; however, studies are limited
    - o Inhibits 5-alpha reductase; anti-inflammatory

| SURGERY |

Indications: BPH resulting in renal insufficiency, recurrent UTI, bladder calculi, or refractory prostatic hematuria; BPH refractory to medication

TRANSURETHRAL RESECTION OF THE PROSTATE (TURP): GOLD STANDARD

- Monopolar: use glycine, water, sorbitol, or mannitol solutions
    - o ***TURP syndrome***: dilutional hyponatremia
        - * Up to 15% of TURPs with < 1% mortality rate
        - * Hypervolemia, hyponatremia, cardiac volume overload,

pulmonary edema, cerebral edema, renal failure (myoglobinemia from RBC lysis)

    - Fluid overload leads to ***hypertension*** with ***reflexive bradycardia***
  - ***Glycine*** converts to ammonia leading to hyperammonemia encephalopathy
    - Hepatic L-arginine coverts ammonia to urea for excretion; however, L-arginine is likely depleted during preoperative fasting. May be given intravenously to limit/decrease ammonia levels.

Glycine

Inhibitory neurotransmitter with retinal and optic nerve toxicity

- Bipolar: uses warm saline, thus reducing the incidence of TURP syndrome
- Risks: hematuria, transfusion, TURP syndrome (more with monopolar), stricture, retrograde ejaculation, erectile dysfunction
  - Most common site of urethral scarring post-TURP is fossa navicularis / meatal stenosis
- Up to 10% of TURP with have incidental prostate cancer found on pathology

TRANSURETHRAL INCISION OF THE PROSTATE (TUIP)

- Incision of prostate at the 5 and 7 o'clock positions
- Indicated for small / normal sized prostates or a tight bladder neck resulting in obstructive symptoms
- Risk: retrograde ejaculation - bilateral incision 15% / unilateral incision 5%
  - Unilateral TUIP is good option for a man with small/normal sized prostate with obstructive symptoms and desires fertility

PHOTOSELECTIVE LASER VAPORIZATION (PVP)

- KTP (potassium-titanyl-phosphate) 532nm vs. Diode 980nm wavelength lasers
- Risks: hematuria, dysuria (usually improves with time), infection
- Improved hemostasis, decreased length of hospital stay, and decreased time of catheterization compared to TURP
- 532nm wavelength is better absorbed by hemoglobin than water
- 980nm wavelength is absorbed by both hemoglobin and water

TRANSURETHRAL VAPORIZATION OF THE PROSTATE (TUVP)

- Monopolar TUVP is ***electrovaporization*** (e.g. VaporTrode™)
- Bipolar TUVP is ***plasma vaporization*** (e.g. PlasmaButton™)
- Risks: hematuria, dysuria (usually improves with time), infection

HOLMIUM LASER ABLATION / ENUCLEATION (HOLAP / HOLEP)

- Holmium:YAG (Yttrium Aluminum Garnet) 2140nm wavelength
  - *o* Highly absorbed in water; therefore, it must be within close tissue contact
  - *o* Not absorbed by hemoglobin
- ***HoLAP***: vaporization of prostatic adenoma
- ***HoLEP***: selectively cutting the prostatic adenoma (similar to a TURP) and removing the adenoma chips at the end of the procedure

TRANSURETHRAL MICROWAVE THERMOTHERAPY (TUMT)

- Heats the prostate, resulting in tissue necrosis and sloughing
- May take up to 6 months for overall treatment effect
- Prostatic median lobe is a relative contraindication
- Risks: infection, urinary retention (prostatic edema), retrograde ejaculation, incontinence (sphincter damage)

TRANSURETHRAL NEEDLE ABLATION (TUNA)

- Transurethral insertion of interstitial radiofrequency needles into the prostate, which produces heat to induce coagulation necrosis
- May take up to 6 months for overall treatment effect

- Best for lateral lobe hyperplasia without a median lobe
- Risks: urinary retention, dysuria (usually self-limiting)
- Long-term outcomes are not as successful as TURP; however, this procedure offers less morbidity

SUPRAPUBIC OR RETROPUBIC SIMPLE PROSTATECTOMY

- Prostatic adenoma enucleation, while maintaining the prostatic capsule
- ***Suprapubic***: incision through the anterior bladder wall
    - Usually preferred approach if median lobe, bladder calculi, or concurrent bladder diverticulectomy
- ***Retropubic***: incision through the prostatic capsule
- Risks: bleeding, transfusion, urinary incontinence (sphincter injury), retrograde ejaculation

CHAPTER 20: IC / PROSTATITIS / CPPS

| INTERSTITIAL CYSTITIS (IC) |

- Diagnosis of exclusion in patients that present with ***urinary frequency, urgency, and pelvic pain***
    - ***Allodynia*** = non-painful stimuli perceived as painful
    - ***Hyperalgesia*** = abnormal heightened sensitivity to painful stimuli
    - May have a decreased bladder capacity (determined under anesthesia)

Interstitial cystitis: patients void to avoid/limit pain

Overactive bladder: patients void to avoid/limit incontinence

- Histology: non-specific findings (i.e. clinical diagnosis), such as mast cell infiltration due to inflammation
    - ***Glycosaminoglycan layer*** disruption
- Originally thought to be exclusively a bladder disorder; however, recent data suggests majority of patients with "interstitial cystitis" actually have a multisystem disorder called ***chronic pelvic pain syndrome (CPPS)***
- Considered to have two types:
    - **Ulcerative type** (~ 10-15%): urothelial ***Hunner's*** ulcerations

        - Tx: cautery of ulceration
    - **Non-Ulcerative type** (~ 85%): painful bladder syndrome / CPPS secondary to pelvic floor dysfunction, abuse (sexual, physical, emotional), anxiety disorders, fibromyalgia, irritable bowel syndrome, or Sjögren's syndrome
- **Pelvic Floor Dysfunction**
    - 85% of patients with chronic pelvic pain syndrome and IC
    - Myofascial strain and hypertonic pelvic muscles may irritate the bladder with increased substance P
    - Pelvic floor contraction leads to dyspareunia, vulvodynia, vaginismus
    - Many have suffered abuse (i.e. emotional, physical, sexual)
    - Dx:
        - Cotton swab test (vulvodynia)
        - Speculum exam, vaginal pH, wet mount (vaginitis)
        - Levator exam at the ischial spine (levator trigger points)
- Tx:
    - If levator palpation reproduces pain: ***myofascial release***
        - May try biofeedback, sacral neuromodulation, posterior tibial nerve stimulation, botulinum toxin type A
        - Avoid Kegel exercises
    - If no levator tenderness or not relieved, but continues with bladder pain, urinary urgency or frequency: treat urothelium with bladder hydrodistention, ***pentosan polysulfate sodium*** (Elmiron®), or intravesical bladder installations (e.g. lidocaine, heparin, Dimethyl sulfoxide (DMSO), pentosan polysulfate sodium)
    - If Hunner's ulcer: lesion ***fulguration***
    - All patients should decrease food triggers such as alcohol, citrus, spicy foods, coffee, soda, tea

| PROSTATITIS |

MEARES-STAMEY FOUR-GLASS PROSTATITIS TEST

- **VB1**: urine from start of void
  - Urine culture of urethra
- **VB2**: midstream urine
  - Urine culture of bladder
- **EPS**: expressed prostatic secretions secondary to prostatic massage
  - Abnormal is > 10 WBCs / hpf
- **VB3**: post-prostatic massage voided urine
  - Urine culture of prostate

NICKEL TWO-GLASS PROSTATITIS (PRE & POST MASSAGE) TEST

- **VB2**: midstream urine
  - Urine culture of bladder
- **VB3**: post-prostatic massage voided urine
  - Urine culture of prostate
- Less cumbersome than 4-glass test, and 96% accuracy

PROSTATITIS CLASSIFICATION

Category	Name	EPS
Infectious		
1	Acute bacterial prostatitis	Acute prostate ***infection***
2	Chronic bacterial prostatitis	Chronic prostate ***infection*** (> 3 months)
Non-infectious		
3	Chronic Pelvic Pain Syndrome (CPPS)	No bacteria Pelvic / prostatic pain UPOINT Classification
3A	Inflammatory CPPS	***WBCs present*** No Bacteria Symptomatic
3B	Non-inflammatory CPPS*	***No WBCs*** No Bacteria Symptomatic
4	Asymptomatic inflammatory prostatitis	***WBCs present*** No Bacteria ***Asymptomatic***

EPS = expressed prostatic secretions

** Previously called prostatodynia*

- ***Type 1 Prostatitis*** is the least common, but most straight forward treatment
- ***Type 3 (CPPS)*** is most common type
- ***Type 4***: no treatment necessary

BACTERIAL PROSTATITIS

- Vast majority of infections are secondary to ***gram negative organisms***; however, men ***< 35 years old*** should be empirically treated for

Chlamydia and ***Gonorrhea***

- Rule out voiding dysfunction/obstruction (e.g. urethral stricture, vesical neck contracture, neurogenic bladder)
    - Consider cystoscopy if recurrent infection or symptoms
- Gentle digital rectal exam is indicated to rule out prostatic abscess
    - If needed, transrectal ultrasound or CT scan may be utilized
- Tx: antibiotic and alpha-blocker
    - Chlamydia/Gonorrhea: doxycycline / ceftriaxone
    - Gram negative bacteria: levofloxacin or 3rd generation cephalosporin ± aminoglycoside

CHRONIC PELVIC PAIN SYNDROME UPOINT CLASSIFICATION

(Category 3 Prostatitis, Interstitial Cystitis, and Painful Bladder Syndrome)

UPOINT	Diagnosis	Treatment
Urinary	Lower urinary tract symptoms; high PVR	Alpha blocker and/or anti-cholinergic
Psychosocial	Clinical depression, or Anxiety disorders	Psychology referral
Organ	Prostate tenderness, WBCs on EPS, or Hematospermia	Quercetin 500mg BID (without vitamin C) Traditional IC treatments
Infection	Positive culture	Antibiotic
Neurologic/Systemic	Systemic chronic pain (i.e. fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome)	Amitriptyline (Elavil®) 10mg (up to 50mg/day), or Pregabalin (Lyrica®) 75mg (up to 150mg/day)
Tenderness	Pelvic floor dysfunction (i.e. pelvic floor spasm or trigger points)	Myofascial release, Biofeedback, or Neuromodulation

CHAPTER 21: URINARY TRACT CALCULI

CALCULI PROMOTERS AND INHIBITORS

Calculi Promoters	Calculi Inhibitors
Protein matrix Oxalate Urate Calcium Low urine pH Low urine volume	Citrate Magnesium Pyrophosphate Glycosaminoglycans Osteopontin
Tamm-Horsfall protein (aka Uromodulin / Uromucoid) may be either a promoter or inhibitor	

| METABOLIC DEFECTS |

HYPERCALCIURIA

1. Absorptive (gut)
2. Renal (kidney)
3. Resorptive (bone)

HYPEROXALURIA

1. Primary (metabolism)
2. Dietary (food)
3. Enteric (gut)

OTHER DEFECTS

1. Hypocitraturia
2. Hyperuricosuria
3. Hypomagnesuria
4. Gouty diathesis
5. Infection calculi
6. Cystinuria
7. Miscellaneous

| CALCIUM BASED CALCULI |

ABSORPTIVE HYPERCALCIURIA

- Increased intestinal absorption of calcium leads to increased renal filtration
- **Type 1: Independent of diet**
    - o Tx: ***Thiazides***, decrease sodium intake, potassium citrate, increase water intake, decrease meat intake; normal intake of calcium
- **Type 2: Dependent of diet**
    - o Tx: ***Thiazides***, decrease sodium intake, potassium citrate, increase water intake, decrease meat intake; reduce calcium intake
- **Type 3: Phosphate leak**
    - o Tx: ***Neutral phosphates***, potassium citrate, increase water intake, decrease meat intake

Pregnancy-related Hypercalciuria

Physiologic absorptive hypercalciuria

RENAL HYPERCALCIURIA

- Distal renal tubule calcium "leakage" into the urine
- Elevated PTH: ***secondary hyperparathyroidism***
- Tx: ***Thiazides***, decrease sodium intake, potassium citrate, increase water intake

RESORPTIVE HYPERCALCIURIA

- Increased bone demineralization leads to increased renal filtration
- Elevated PTH: ***primary hyperparathyroidism***
- Etiology of ***paralyzed*** or ***bedridden*** patients
- Tx: ***parathyroidectomy (adenoma or hyperplasia), bisphosphonates***, orthophosphate, potassium citrate, increase water intake

HYPERCALCIURIA LAB FINDINGS

Lab	Absorptive	Renal	Resorptive
Serum Calcium	Normal	Normal	↑
Fasting Urine Calcium	Type 1: ↑ Type 2: normal	↑	↑
PTH (Urine cAMP)*	↓	↑	↑
Intestinal absorption	↑	↑	↑

** PTH is commonly measured as Urine cAMP.*

PRIMARY HYPEROXALURIA

- Hepatic enzyme deficiencies lead to increased production of oxalate that results in increased renal filtration
- Urinary calculi in pediatric patients and may lead to ESRD
- **Type 1**
    - o ***Alanine-glyoxylate aminotransferase (AGT)*** deficiency
        - * Leads to glyoxylate conversion to oxalate and glycolic aciduria
    - o Autosomal recessive, Chromosome 2
    - o Pyridoxine (Vitamin B6) is a reaction cofactor
- **Type 2**
    - o ***Glyoxylate reductase and hydroxypyruvate reductase (GRHPR)*** deficiency
        - * Leads to L-glyceric aciduria
    - o Autosomal recessive, Chromosome 9q12, very rare
    - o Pyridoxine is not a reaction cofactor
- **Type 3**
    - o ***4-hydroxy-2-oxoglutarate aldolase 1 (HOGA1)***; formerly DHDPSL deficiency
    - o Autosomal recessive, Chromosome 10q24, extremely rare

- Tx: ***liver and renal transplant*** (for all types), ***Vitamin B6 supplementation***, low oxalate diet, decrease vitamin C intake, increase water intake

DIETARY HYPEROXALURIA

- Increased dietary intake of oxalate
- Common high oxalate foods: lemon and lime peel, rhubarb, spinach, collards, okra, parsley, leeks, nuts, seeds, wheat bran, chocolate, black tea, raspberries, concord grapes, green beans, celery
- Tx: ***avoid/limit the above foods, Vitamin B6 supplementation***

ENTERIC HYPEROXALURIA

- Increased intestinal absorption of oxalate leads to increased renal filtration
- Associated with ***inflammatory bowel syndrome, Crohn's disease, chronic pancreatitis, short gut syndrome, bariatric surgery, celiac sprue***
    - Bile salts are usually absorbed in the terminal ileum, and in the above diseases, results in decreased bile salt absorption. This leads to increased bile salt / calcium chelation within the intestine, allowing increased absorption of non-calcium bound oxalate within the colon.
- Associated with ***chronic antibiotic usage***
    - Decreases ***oxalobacter formigenes***, which normally metabolizes oxalate (up to 50%) in the intestines
- Tx: ***low fat / oxalate diets***; ***oral calcium supplementation*** (increases calcium-oxalate chelation), ***Vitamin B6 supplementation***, bile salt resins, reverse gastric bypass, increase water intake, potassium citrate

HYPOCITRATURIA

- Decreased hydrogen-citrate chelation results in acidic urine
- Decreased calcium-citrate chelation results in hypercalciuria
- Associated ***metabolic acidosis*** leads to citrate movement into the mitochondria to chelate with hydrogen, resulting in decreased urine citrate.

- Below are several conditions that result in metabolic acidosis.
  - o ***Distal RTA (type 1)***
    - * Inability for renal distal tubule hydrogen secretion that results in metabolic acidosis and paradoxical ***basic urine*** (i.e. inability to acidify urine)
    - * Majority ***females***; presents 20-30 years of age
    - * Lab: 2nd morning fasting void (1st void affected by pre-fasting diet), ***hypokalemia*** (elevated aldosterone), hypocitraturia, metabolic acidosis, urine pH > 5.5, hyperphosphaturia (bone demineralization)
    - * Associated with ***calcium phosphate calculi, medullary sponge kidney, nephrocalcinosis***
    - * Incomplete distal RTA: no/mild acidosis with low-normal potassium
      - Lab: ***ammonium chloride loading test*** (unable to acidify urine is a positive result)
  - o Chronic diarrhea (bicarbonate loss)
  - o Thiazide (causes intracellular acidosis)
  - o High dietary protein (acid ash diet)
  - o Excessive exercise (lactic acidosis)
- Tx: ***Potassium citrate***, increase water intake

HYPERURICOSURIA

- Increased uric acid renal filtration caused by:
  - o High dietary purines (organ meat, beer)
  - o Gout
  - o Tumor lysis syndrome (increased cell turnover secondary to chemotherapy)
- pKa uric acid = 5.5
  - o If urine ***pH < 5.5***, then ***uric acid calculi***
  - o If urine ***pH > 5.5***, then ***calcium oxalate calculi***
- ***Monosodium urate*** is a nidus for calcium oxalate calculi
- Tx: ***Allopurinol*** (inhibits xanthine oxidase thus decreases uric acid;

however, increases xanthine, which may lead to xanthine stones), ***potassium citrate***, increase water intake

  - Potassium citrate may dissolve existing uric acid calculi

HYPOMAGNESURIA

- Decreased magnesium renal filtration leads to decreased magnesium-oxalate chelation; results in calcium oxalate calculi
- Decreased magnesium also leads to hypocitraturia (unknown mechanism)
- Rare as a solitary defect (< 1%); however, may commonly be associated with inflammatory bowel disease
- Tx: ***magnesium citrate***, increased water intake, potassium citrate
  - Magnesium side effects: flushing, diaphoresis, diarrhea
  - Magnesium toxicity: hypotension, bradycardia, hypothermia, respiratory depression

| NON-CALCIUM BASED CALCULI |

GOUTY DIATHESIS = ACIDIC URINE

- ***Insulin resistance*** leads to decreased ammonium, thus increased urine titratable acids
  - Interstitial glutamine → alpha- ketoglutarate and Ammonia (NH3); then proximal tubular Ammonia binds hydrogen → Ammonium (NH4), which allows for renal excretion of hydrogen without lowering urine pH
    - Metabolic acidosis and alkaline urine will develop without this renal reaction, which may ultimately lead to uric acidosis and bone demineralization
- Usually form ***uric acid calculi***; however, may form ***calcium oxalate calculi***
- Risks: ***diabetes, gout***
- In all mammals ***uricase*** converts uric acid to allantoin (more soluble), except humans and Dalmatians, which lack uricase
- Tx: ***potassium citrate***, increase water intake, allopurinol, low sodium diet

Urine Alkalization

Closely monitor urine pH for over-alkalization to avoid calcium phosphate calculi formation

INFECTION CALCULI

- Calculi are formed by the presence of urealytic UTIs via ***urease***
    - o Urea + urease + water = 2 **Ammonia** (NH3) + CO2 then
    - o Ammonia + water = **Ammonium** (NH4) + OH resulting in ***alkaline urine***. This increased pH leads to decreased phosphate solubility, and calculi.
    - o Urine pH > 7.2
- Most common bacteria: ***Proteus, Klebsiella, Pseudomonas***, Staphylococcus (extremely rare for E. coli to be the etiology)
- Composed of ***Struvite (magnesium-ammonium-phosphate)*** or ***carbonate apatite (calcium phosphate)***, staghorn calculi
    - o Struvite: ***Coffin-lid crystals***

Struvite Coffin-lid Crystals Mnemonic

Struvite infected stones can result in death; therefore, coffin-lid shaped

- Tx: complete calculi removal is key, correct any anatomic / functional abnormalities
    - o Acetohydroxamic acid: urease inhibitor (SE: hemolytic anemia, phlebitis); rarely used

CYSTINURIA

- Autosomal recessive; defective reabsorption of dibasic amino acids in the renal ***proximal*** tubule and small intestine
    - o Dibasic acid = COLA: cystine, ornithine, arginine, lysine
        - * Only cystine is not urine soluble
- Types A (SCL3A1 gene), B (SLC7A9 gene), **AB** (SLC3A1 gene; AB type is the main etiology of cystine calculi)
- ***Hexagon crystals***
- Cystine stones from in acid urine
- Lab: 24 hour urine or ***sodium cyanide–nitroprusside test***
    - o Cystine (urine) + cyanide = cysteine, then
    - o Cysteine + nitroprusside = ***red-purple color change***
- Tx: low methionine diet, potassium citrate, increase water intake
    - o Chelation: binding agents that result in increased solubility
        - * ***Thiola (alpha-mercaptopropionylglycine)*** – 1st line due to decreased side effects
        - * Penicillamine
            - Side effects: thrombocytopenia, B6 deficiency, nephrotic syndrome
        - * Captopril
            - Captopril-cystine bond is much more soluble, but unreliable
    - o ***Decrease urinary cystine daily output to < 250 mg/L*** (above this volume, cystine precipitates out of solution)

MISCELLANEOUS

- **Matrix Calculi**
    - o Uncommon; approximately 65% of calculus is composed of organic material
        - * ***Mucoprotein*** (protein; 2/3)
        - * ***Mucopolysaccharide*** (carbohydrate; 1/3)
    - o Radiolucent calculi; however, it may have a calcified peripheral rim

  - Often mistaken for collecting system tumors or blood clots
- **Xanthine Calculi**
  - Defective xanthine dehydrogenase (XDH) or xanthine oxidase (XO) results in elevated xanthine levels
  - Hypoxanthine + XDH = Xanthine; Xanthine + XDH = urate
    - * In ischemic conditions: XDH converts to XO, and XO replaces XDH in the above pathway.
  - Allopurinol inhibits XDH, and may cause increase xanthine levels and xanthine calculi
- **Lesch-Nyhan Syndrome Uric Acid Calculi**
  - X-linked recessive
  - Hypoxanthine-guanine phosphoribosyltransferase deficiency leads to hyperuricemia and hyperuricosuria, resulting in uric acid calculi
- **Ammonium Urate Calculi**
  - Etiology: urealytic UTI, laxative abuse, ileostomy
  - May form ammonium urate (basic urine) or uric acid stones (acid urine)
- **Medications**
  - Guaifenesin, Ephedrine, Triamterene, Topiramate, Indinavir, Ciprofloxacin, Sulfa medications, Acetazolamide, Ceftriaxone (pediatric patients)
  - ***Loop Diuretics***: calcium oxalate
    - * Hypercalciuria seen in infants (switch to thiazide)
  - Avoid excessive vitamin intake, as these can potentiate stone formation
- **Pregnancy**
  - ***Physiology absorptive hypercalciuria*** secondary to placental Vitamin D secretion
  - ***Hypercitraturia*** in 3rd trimester to counter physiologic absorptive hypercalciuria; therefore, the ***risk of calculus formation during pregnancy is not increased!***
  - Tx: medical expulsion treatment; however, ureteroscopy with Holmium laser is becoming more popular. If a stent is placed,

it should be changed every 4 weeks because of early stent encrustation. Percutaneous nephrostomy is also an option.

- **Randall's plaques**
  - Renal medullary crystallization within the subepithelium that erodes through the papilla to act as a nidus for nephrolithiasis
- **Obesity, hypertension, and diabetes**
  - All are associated with increased risk of nephrolithiasis
  - Metabolic syndrome leads to decreased urinary pH (Gouty Diathesis)
  - Tx: weight loss, decreases sodium, improved glucose control, thiazides
- **Bladder augmentation related bladder calculi**
  - Nidus for calculus formation is mucus
  - Tx: daily bladder irrigation
    - * Antibiotics, potassium citrate, sodium restriction is not helpful

SUMMARY OF URINARY CALCULI FINDINGS

Calculi	Urine pH	Radio -opaque or -lucent	Crystals
Cystine	Acidic	Poorly opaque	Hexagon
Uric Acid	Acidic	Lucent	Pleomorphic
Xanthine	Acidic	Lucent	Small, round/oval
Matrix	Acidic	Lucent	Variable
Indinavir	Neutral/Basic	Lucent *	Rectangle, star-burst, fan
Ammonium urate	Neutral/Basic	Lucent	Thorn apple (prickly sphere)

Calculi	Urine pH	Radio -opaque or -lucent	Crystals
CaOx – monohydrate (Whewellite)	Neutral	Opaque	Rod/Dumbbell
CaOx – Dihydrate (Weddellite)	Neutral	Opaque	Envelope
MAP (Struvite)	Basic	Opaque	Coffin-lid
CaPhosphate (Apatite, Brushite)	Basic	Opaque	Amorphous

CaOx = Calcium Oxide; MAP = Magnesium Ammonium Phosphate

** Protease inhibitors are not visible on CT scan*

| HOW THE TREATMENTS WORK |

- **Thiazide**: inhibits distal tubule sodium secretion
  - Sodium follows calcium; therefore, reduced calciuria
  - Side effects: ***hypocitraturia***, ***intracellular acidosis***, hypokalemia
    - * Potassium citrate may be needed to negate thiazide side effects
  - Consider drug holiday as effect decreases over time, but is regained with a drug holiday
- **Reduce Sodium intake**: leads to decreased renal sodium secretion into the urine, thus reduced calciuria (calcium follows sodium)
  - Extremely important for stone reduction, and thiazides treatment
- **Potassium Citrate**: urinary alkalization; citrate binds urinary hydrogen and calcium (calcium not available to bind oxalate in the collecting system)
  - If gastrointestinal intolerance or bowel movement with undigested tablets, switch to liquid preparation

- **Orthophosphates**: intestinal calcium chelation
- **Neutral phosphates**: increases phosphate, which is an inhibitor of vitamin D and intestinal calcium absorption
- **Decreased red meat intake**: animal protein digestion results in high purine turnover; decreased red meat leads to decreased purine turnover and urine amino acid levels, thus an increased urine pH
    - o Adkin's Diet (high protein, low carbohydrate): hypercalciuria, hyperuricosuria, hypocitraturia, acidic urine
- **Decreased oxalates**: decreases available oxalate to bind calcium
- **Vitamin B6**: cofactor to allow oxalate breakdown
- **Increase water intake (urine output > 2L/day)**: dilution of urinary solutes and increases urinary pH
- **Limit excessive Vitamin C**: excessive vitamin C is converted to oxalate
- **Bile resin salts**: binds intestinal bile salt, which allows more calcium to bind oxalates within the intestines
- **Calcium supplement**: increased intestinal oxalate binding
    - o Important for any patient with irritable bowel syndrome and short gut-like conditions (e.g. gastric bypass)
- **Avoid hyperglycemia**: hyperglycemia may lead to ketoacidosis
- **Allopurinol**: inhibits xanthine oxidase and reduces uric acid production
    - o Indications: gout and hyperuricosuria

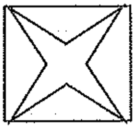
| METABOLIC WORKUP |

- Urinary Analysis
    - o pH may help identify stone type
        - * ***pH < 5 is likely uric acid calculi***
        - * ***pH > 7 is likely infection calculi***
        - * Metabolic acidosis with basic urine pH is likely RTA 1
    - o ***Brushite (calcium hydrogen phosphate)***: form in more acidic

    urine (pH 6.5-6.8) in conjunction with hypercalciuria and hyperphosphaturia. If pH rises to > 6.8, the calculus transitions to carbonate apatite
  - ***Carbonate apatite***: form in more alkaline urine (pH > 6.8) in conjunction with hypercalciuria and hypocitraturia
- Serum electrolytes, creatinine, calcium, uric acid, parathyroid hormone, and phosphorus
  - RTA 1: hypokalemia, metabolic acidosis
  - Renal or resorptive hypercalcemia: elevated PTH
  - Gout diathesis / Gout: elevated uric acid
  - Absorptive hypercalciuria type 3: low serum phosphate
- Requires 24 hour urine collection
  - Confirmation: ***urine creatinine*** (***~ 1 mg / kg / hour***)
    - Men: 20-25 mg / kg / day
    - Women: 15-20 mg / kg / day
- Increased urine uric acid after taking potassium citrate
  - ***The previous crystalized uric acid at an acidic pH becomes soluble at the increased urine pH***
- Continued acidic urine after taking potassium citrate
  - Patient non-compliance
  - Confirmation: urine potassium
- Urinary diversion
  - Results are inaccurate; treat empirically with potassium citrate

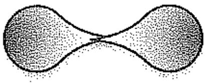
URINARY CALCULI MICROSCOPY

CALCIUM OXALATE DIHYDRATE



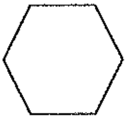
Envelope

CALCIUM OXALATE MONOHYDRATE



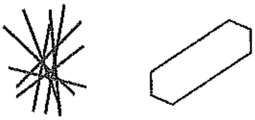
Dumbbell

CYSTINURIA



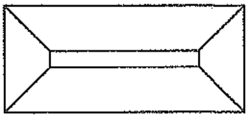
Hexagon

URIC ACID



Pleomorphic

MAGNESIUM AMMONIUM PHOSPHATE



Coffin-lid

| SURGICAL TREATMENT |

EXTRACORPOREAL SHOCK WAVE THERAPY (ESWL)

- Main mechanism of action to fracture calculi is ***cavitation***
- May induce irreversible nephron injury that forms a scar, as well injury to small and medium vessels that leads to subcapsular hematoma
- ***Primer setting***: by starting at a low energy setting for a short period of time, followed by withholding shockwaves for 3-4 minutes, then increasing the energy setting will decrease renal injury
- Decrease efficacy: increasing diameter, lower pole location, multiple calculi
- Increased efficacy: progressive increasing energy, lower rate
- Side effects: bacteremia (< 15%), sepsis (< 1%), steinstrasse (< 5%), residual stones, renal hematoma, hematuria, diastolic hypertension, transient decrease in GFR, cardiac arrhythmias (reduced with ***gating*** – firing shock waves only on the cardiac R-waves)
- Contraindications: pregnancy, bleeding diathesis (e.g. liver disease), acute UTI, uncontrolled hypertension

PERCUTANEOUS NEPHROLITHOTOMY (PCNL)

- Treatment of choice for ***staghorn calculi, large calculi (> 2cm), extensive stone burden,*** or ***ESWL-refractory***

Calculi Resistant to ESWL

Calcium oxalate monohydrate, cystine, calcium phosphate (Brushite), matrix

Treatment of choice: PCNL

- Optimal approach for solitary stone is directly into the respective calyx or a ***posterior***, inferior calyx for staghorn calculi
    - o Posterior calyces are the safest approach with decreased risk for a significant bleed

  - If entry is directly into the infundibulum or renal pelvis, do not use this access. Re-attempt calyceal access.

PCNL Bowel Injury (Retro-renal colon)

(1) Nephrostogram shows contrast within the colon

(2) Stop procedure

(3) Retract nephrostomy and maintain within the colon for 7-10 days

(4) Insert ureteral stent

(5) Low residue diet and antibiotics

(6) Repeat "nephrostogram"; remove tube if no evidence of extravasation or fistula

- ***Collecting system perforation***
  - 1st sign: narrow pulse pressure (decreased venous return secondary to compression of the IVC by extravasated retroperitoneal fluid)
  - Later: ventilation difficulty → hypercarbia; elevated central venous pressure
  - Hypotension only if significant hemorrhage
  - Abdominal distension will only be noted when supine (i.e. not in prone position)
- If sepsis occurs post-PCNL, culture calculus for likely bacteria culprit
  - Sepsis rate is not related to length of procedure, stone-free rate, nor subcostal vs. supracostal access
- If delayed bleed, most likely secondary to a pseudoaneurysm or AV-fistula
  - Hemodynamic stability: tamponade catheter, pRBC transfusion
  - Hemodynamic instability: angiography with selective arterial embolization; emergent nephrectomy
- ***Horseshoe Kidney***

  - o Upper pole calyces face posterior and lateral
    - * Good access point (inferior calyces are difficult to access)
- ***Ectopic and transplant kidney***
  - o May need a laparoscopic approach to gain calyceal access

ANATROPHIC NEPHROLITHOTOMY

- Renal parenchymal incision at Brodel's avascular line, and subsequent removal of nephrolithiasis / staghorn
- Large stone burden, and PCNL is contraindicated, or has failed
- Open, laparoscopic, or robotic

DISEASES ASSOCIATED WITH RENAL CALCULI

Disease	Metabolic Defect	Calculus Type
Diabetes	Gouty diathesis	Uric acid, Calcium oxalate
Ileostomy	Acidosis (bicarbonate loss)	Uric acid
IBD (Crohn's disease), Roux-n-Y	Hypocitraturia, hyperoxaluria (saponification), acidic urine, metabolic acidosis, hypomagnesuria	Calcium oxalate
Distal RTA	Hypocitraturia, acidic urine	Calcium phosphate
Hyperparathyroidism	Resorptive hypercalciuria	Calcium-based
Hypothyroidism	Hypercalciuria	Calcium-based
Cystic fibrosis	CFTR gene	Medullary nephrocalcinosis
Bedridden	Resorptive hypercalciuria	Calcium oxalate

CHAPTER 22: URETHRAL DISEASE

| URETHRAL STRICTURES |

Urethral stricture: circumferential spongiofibrosis (scar) of the anterior urethra

Urethral contracture/stenosis: posterior urethral lumen contraction from fibrosis

Urethral distraction/defect: membranous urethra disruption (i.e. avulsion of the bulbomembranous junction) related to pelvic fractures

- 10-20% of urethral distractions will have concomitant bladder injury
- Commonly associated pelvic injury pattern: pubic symphysis diastasis or fracture and/or sacroiliac diastasis

MEATAL STENOSIS: NARROWING OF THE FOSSA NAVICULARIS

- Most common etiology in pediatrics: circumcision
  - Tx: ventral meatotomy
- Most common etiology in adults: transurethral manipulation
  - Tx: dilation (particularly if poor surgical candidate), meatotomy, meatoplasty, urethroplasty
- Sx: urine spraying/splitting, dysuria

ETIOLOGY

- Trauma: usually blunt trauma secondary to motor vehicle accident or straddle injury
- Iatrogenic: any urethral manipulation, hypospadias repair, TURP, or catheterization from pressure ischemia or traumatic insertion

- Infectious (e.g. gonococcal urethritis)
    - o Cowper's gland may contribute to location of infection; bulbar secretion
- Inflammatory (e.g. lichen sclerosis / balanitis xerotica obliterans): Koebner phenomenon – latent dermatic response to inflammation
- Post-cardiac surgery
    - o Post-cardiac bypass results in stricture in up to 20% of patients
- Congenital: stricture is composed of ***smooth muscle*** rather than inflammation / fibrosis
    - o ***Cobb's Collar*** (aka ***Moorman's Ring)***: congenital bulbar urethral narrowing
        - * Unknown etiology but possibly from urogenital diaphragm or cloacal membrane persistence; may lead to urethral stricture
        - * Normal, common variant seen on VCUG
- Post-penile or pelvic radiation
- Idiopathic

PATHOLOGY

- Dense fibrosis of the corpus spongiosum with an intact urothelium
- Urethral irritation leads to urothelium breakdown with subsequent urine extravasation into the corpus spongiosum. This leads to fibrosis and ultimately to stricture formation.
- Most commonly found in the bulbar urethra
    - o Lichen sclerosis / BXO are most common at the meatus and distal urethral

SYMPTOMS

- ***Spraying stream***, weak stream, dribbling, incomplete bladder emptying, hematuria, incontinence, abdominal (valsalva) voiding
- Sequelae
    - o Signs of bladder outlet obstruction with high voiding pressure
        - * Trabeculation, bladder wall hypertrophy, bladder calculi, hydronephrosis

  - Urinary retention
  - Infection (UTI, prostatitis, epididymo-orchitis, periurethral abscess, sepsis)
  - Urethrocutaneous fistula

"Watering Can Perineum"

Bulbar urethral stricture resulting in urethrocutaneous fistula(s)

WORKUP

- **Uroflow**: plateau flow curve or intermittent flow curve
  - Usually decreased Qmax and increased PVR
- **Ultrasound**: study of choice for urethral strictures
  - Excellent at determining length of stricture and determine ***spongiofibrosis***
- **Retrograde urethrogram (RUG)**: illustrates stricture and associated extravasation
  - Do not confuse increased membranous urethral tone with a urethral stricture
  - **VCUG**: allows visualization of proximal urethral and bladder disease
- **Cystoscopy**: evaluates the luminal diameter with possible concomitant RUG and direct visual internal urethrotomy
- Check for prepuce on physical exam, as this may be utilized during reconstruction

TREATMENT

Consider stricture ***biopsy*** if:

- History of genitourinary malignancy
- Recurrent stricture
- Abnormal appearing stricture

OBSERVATION

- May be considered if incidental, asymptomatic, and low PVR; however, as a stricture lengthens, there is an increase in treatment failure

DILATION

- Goal is gentle, progressive dilation, not tearing of the stricture / mucosa, as this will increase recurrence (usually ≤ 24F)
- Similar efficacy of DVIU
    - < 2 cm: 40% failure at 1 year
    - 2-4 cm: 50% and 75% failure at 1 and 4 years, respectively
    - > 4 cm: 80% failure at 1 year
- **The French (Fr) Unit**
    - 1 Fr = 0.33 mm diameter (e.g. 18 Fr Foley has a 6 mm external diameter)
    - French ≈ Circumference (e.g. 18 Fr Foley has a 18 mm circumference)

DIRECT VISUAL INTERNAL URETHROSTOMY (DVIU)

- Cold-knife or Holmium laser 12 o'clock urethral stricture incision
    - Consider incision at 4 and 8 o'clock to reduce incidental corpora cavernosal injury with subsequent erectile dysfunction
    - DVIU at the meatus should be done at the 6 o'clock position
- Foley catheter for 3-5 days post-operatively
- ***Repeat DVIU nears 100% failure rate at 48 months***
    - Presence of spongiofibrosis increases DVIU failure rate
    - Repetitive DVIU may decrease future urethroplasty success

Urethral Stricture Initial Treatment

DVIU or dilation will successfully treat ~ 50% of all short strictures

INTRAURETHRAL STENT

- Braided mesh cylinder to open the urethral lumen radially
- Indication: (1) recurrent bulbar urethral strictures, (2) BPH, and (3) detrusor sphincter dyssynergia (alternative to sphincterotomy)
    - Usually reserved for poor surgical candidates
- Contraindication: urethral strictures < 24Fr untreated; UTI; prostate, urethral, or bladder cancer; untreated BPH
- Side effects: high rate of UTI; stent migration; recurrent stenosis; reoperation with tandem stent or removal

Recurrent Stricture After DVIU / Dilation

Proceed to urethroplasty, as repeat DVIU / dilation has an extremely high recurrence rate

URETHROPLASTY

- Two categories of urethroplasty: anastomotic or substitution

END-TO-END ANASTOMOSIS

- Resect the stricture, spatulate urethral ends, and primary tension-free anastomosis
    - Critical to preserve bulbar arterial supply during mobilization
- Tension-free anastomotic options:
    - Urethral mobilization of penile suspensory ligament
    - Separation of proximal corporeal bodies
    - Inferior pubectomy
    - Re-route urethra lateral to corporal body
- Recommended for strictures ***< 2-3 cm*** in the ***bulbar*** urethra (recurrence rate ~ 5%); may consider in ***< 1 cm*** in the ***pendulous*** urethra with caution as it may cause ventral chordee

BUCCAL MUCOSAL GRAFT URETHROPLASTY

- Buccal mucosa is harvest from the oral cavity and grafted into the urethra
- Dorsal vs. ventral-onlay to the urethra is controversial, but both have good and similar success rates
    - Commonly, the pendulous urethra is a ***dorsal-onlay***; while the ***ventral-onlay*** is reserved for bulbar. These methods represent the spongiosum anatomy and areas of greater thickness throughout the urethra (i.e. potential blood supply)
- Recommended for strictures:
    - In the ***bulbar*** urethra ***> 2-3 cm***
    - In the ***pendulous*** urethral ***< 2 cm,*** that fail a one-time DVIU / dilation
    - In the ***pendulous*** urethra ***> 2 cm***
    - ***Fossa navicularis***
- Bulbar urethral stricture > 2cm success rate ~ 75%
- Pendulous urethral stricture success rate ~ 85%

JOHANSON 2-STAGE URETHROPLASTY

- Indicated for long strictures that buccal mucosal graft onlay alone would be insufficient; anterior urethrocutaneous fistula (excised at 1st staged, then allowed to heal)
- 1st stage: incise the urethra ventrally, and suture the everted urethral edge to ventral penile skin (i.e. bring the meatus proximally). May include buccal mucosal graft at this stage if narrow urethral plate
- 2nd stage: 3-6 months later a "U"- incision is made and a new tubular urethra is reconstructed once the urethral plate is 30mm; otherwise cut "U" incision wider or add a buccal mucosal graft

FLAP URETHROPLASTY

- Penile skin vs. prepuce vs. de-epithelized scrotal skin
    - Dartos fascia is base of the flap
    - ***External pudendal artery*** supplies the prepuce, penile and scrotal skin

- Utilized usually for distal urethral strictures
- Increased recurrence and complication rates

PERINEAL URETHROSTOMY

- Consider in patients with recurrent, failed urethroplasty

SUPRAPUBIC CYSTOSTOMY, INDWELLING FOLEY CATHETER, OR SELF-CATHETERIZATION

- Consider in patients that refuse or are non-surgical candidates

Urethroplasty Diameter Goal

30+ mm urethral plate is desired to reconstruct at least a 30 Fr urethra

URETHROPLASTY COMPLICATIONS

- Recurrent stricture, onlay diverticulum, decreased glans sensation, cold glans, ejaculatory dysfunction, urinary incontinence, infection, urethrocutaneous fistula, Stensen's duct injury during buccal mucosa harvest

URETHRAL STRICTURE TREATMENT SUMMARY

Location	Length	Treatment Considerations
Meatal Stenosis – Adult	---	Dilation, meatotomy, meatoplasty, or urethroplasty
Meatal Stenosis – Pediatric	---	Ventral meatotomy
Bulbar urethra	< 2-3 cm	DVIU; if fails, end-to-end urethroplasty
Bulbar urethra	> 2-3 cm	Buccal mucosal graft urethroplasty
Pendulous urethra	< 1cm	DVIU; if fails, may consider and end-to-end urethroplasty
Pendulous urethra	< 2 cm	DVIU; if fails, buccal mucosal graft urethroplasty
Pendulous urethra	> 2 cm	Buccal mucosal graft urethroplasty or Johanson urethroplasty ± buccal mucosal graft
Posterior urethra	< 3 cm	Perineal anastomotic urethroplasty
Posterior urethra	> 3 cm	Abdominal transpubic perineal urethroplasty
Bladder neck contracture	---	Transurethral vesical neck incision or resection at 5 and 7 o'clock; dilation; if fails, abdominal transpubic perineal urethroplasty
Prior hypospadias repair	---	Johanson urethroplasty ± buccal mucosal graft
Lichen sclerosis	---	Johanson urethroplasty ± buccal mucosal graft
Failed multiple urethroplasties	---	Perineal urethrostomy (1st failure, may consider one time DVIU)
Surgically unfit or refuse surgery	---	Suprapubic cystostomy

Pendulous Urethral End-to-End Anastomosis

If > 1cm, may lead to ***chordee*** and penile shortening; therefore, only use in very short pendulous strictures.

URETHRAL DIVERTICULUM

- Urethral outpouching
- Thought to be associated with obstructed / infected periurethral glands
- More common in females
- Rarely associated with urethral carcinoma (hematuria)
- Sx: postvoid dribbling, dyspareunia, dysuria, UTI, urgency, frequency
- Physical exam: anterior vaginal wall or periurethral mass
  - Majority distal urethra and dorsolaterally
- Imaging: VCUG, ***MRI*** (imaging of choice)
- Tx: diverticulectomy or marsupialization
  - If concurrent stress urinary incontinence, avoid synthetic midurethral slings, and use fascia or dermis slings.

Urethral Diverticulum "3 D's"

Dysuria, Dyspareunia, Dribbling

URETHRAL CARUNCLE

- Benign, distal urethral granulomatous lesion that appears as a reddish, fleshy lesion on the urethral meatus
  - ***Usually posteriorly*** and ***not circumferential***
- Vast majority in ***post-menopausal women***

- Associated with ***estrogen deficiency***
- Sx: hematuria, dysuria, dyspareunia
- Tx: estrogen cream; surgical resection
  - If asymptomatic, observe

| URETHRAL PROLAPSE |

- Benign, ***circumferential*** urethral protuberance via the meatus
- Increased intra-abdominal pressure leads to separation of inner and outer urethral layers, and results in prolapse
- Sx: bleeding, irritation
- Tx: surgical resection (mandated if strangulation)
  - Medical Tx: sitz bath, topical estrogen cream, topical antibiotic cream

Urethral Caruncle vs. Prolapse

Caruncle: usually posterior; not circumferential

Prolapse: circumferential

CHAPTER 23: UPPER URINARY TRACT TRAUMA

Trauma grading scales:
http://www.trauma.org/archive/scores/ois.html

| ADRENAL TRAUMA |

- Adrenal trauma is very uncommon; however, when present it is associated with severe organ injuries and increased mortality
- Adrenal evaluation via CT scan with IV contrast or direct inspection
- Right sided injuries more common (usually associated with liver trauma)
- Injuries are usually self-limited; only a minority will need adrenalectomy or chronic steroid therapy

| RENAL TRAUMA |

- Mechanism of injury and hematuria are the best indicators for renal evaluation
- ***However the degree of hematuria does not consistently indicate the severity of the renal injury***
- Vast majority (~ 95%) of renal injuries are Grade 1 (subcapsular hematoma)

Trauma Triad of Death

Hypothermia, Acidosis, Coagulopathy

- **CT scan with contrast** is the gold standard for renal trauma imaging. If any renal abnormalities are noted, add CT scan delay images to assess the collecting system and ureter.
- CT scan is indicated in the following situations, assuming the patient is stable enough imaging

1. Significant mechanism of injury (consider if rapid deceleration, all penetrating trauma, and flank trauma)
2. Gross hematuria
3. Microscopic hematuria and hypotension (systolic pressure < 90 mmHg)
4. All pediatric patients with microscopic or gross hematuria

NOTE: *the previous pediatric cutoff for microscopic hematuria was 50 rbc/hpf; however, degree of hematuria in the pediatric trauma setting has a poor correlation to the severity of renal injury*

Renal imaging is not indicated if microscopic hematuria without hypotension in adults; as it is extremely rare to have significant renal injury

- CT scan findings of significant concern:
  - o Renal parenchymal non-enhancement (renal artery injury)
    - * ***Cortical rim sign***: peripheral renal enhancement secondary to capsular arteries; however, no parenchymal blood flow
  - o Medial hematoma (renal hilum injury)
  - o Medial contrast extravasation (ureteropelvic junction injury)

    - o Hematoma > 3.5cm thick (large bleed)
    - o Vascular contrast blush (active bleeding)
- If the patient is not stable enough for a CT scan, then immediate surgical exploration will be required.
    - o ***Single-shot IVP*** performed on the operating table
        - * 2 mg/kg IV contrast
        - * Single abdominal x-ray 10 minutes post-contrast injection
        - * If significantly abnormal, will need renal exploration
        - * Determines presence / absence of contralateral kidney
- Renal trauma grading essentials
    1. Hematuria with normal findings; subcapsular hematoma
    2. Perirenal hematoma; < 1cm laceration
    3. > 1cm laceration (no urinary extravasation)
    4. Laceration with urinary extravasation (i.e. collecting system injury); contained renal hilum injury
    5. Shatter kidney; hilar avulsion

CONSERVATIVE MANAGEMENT

- Stable patients with ***grade 1-3 renal trauma should be managed non-operatively*** with close hemodynamic monitoring
    - o Serial hemoglobin / hematocrit
    - o Bed rest while gross hematuria present
- Many grade 4 and possibly some grade 5 renal trauma patients that are hemodynamically stable may also be managed non-operatively
- In grades 2-4, up to 25% of patients may experience a delayed bleed
- Ureteral stent may be beneficial if collecting system injury (grade 4) is suspected
    - o If during observation urine extravasation continues on surveillance CT scan, a ureteral stent is indicated
- **Renal Arteriography**
    - o Superselective embolization to cease persistent arterial bleed in stable patients, such as those undergoing conservative management or have delayed bleeding

  - Arteriovenous fistula and pseudoaneurysms may be created as a result of renal trauma, and may also be embolized to prevent hemorrhage
  - Renal artery stenting for acute (< 6 hours) thrombosis from intimal tear may be performed in the hemodynamically stable patient; otherwise, there is a high incidence of nephrectomy

SURGICAL EXPLORATION

- ***Renal exploration (transabdominal) is required if:***
  - Renal injury with hemodynamic instability
  - Expanding, pulsatile renal hematoma
  - Renal hilar avulsion
  - Ureteropelvic junction disruption

Retroperitoneal Hematoma

If noted intraoperatively, but it is nonexpanding, do not explore retroperitoneum...manage conservatively

- ***Proximal hilar control*** is imperative prior to opening Gerota's fascia because once the hematoma loses tamponade, perfuse bleeding may occur making it difficult to salvage the kidney and prevent major blood loss
  - The transverse colon is placed on the chest
  - Small bowel / mesentery are place superiorly and to the right, thus exposing the retroperitoneum over the aorta
  - Incise the retroperitoneum directly over the aorta from the inferior mesenteric artery to the Ligament of Treitz (approximately the superior mesenteric artery), while staying medial to the inferior mesenteric vein (runs longitudinally in the left colonic mesentery)
- Evaluation of the kidney: renorrhaphy, partial nephrectomy or nephrectomy

COMPLICATIONS ASSOCIATED WITH RENAL TRAUMA

- ***Page Kidney***: hematoma, urine, and scar compress the renal parenchyma leading to hypertension
- ***Urinoma***: ureteral stent may decrease formation
- ***Perinephric infection* / abscess**: prophylactic antibiotics are not proven to decrease infection; however, clinically they are routinely prescribed
- ***Delayed renal bleed***: close observation is imperative
  - Usually occurs within 3 weeks of the trauma
- ***Arteriovenous fistula and pseudoaneurysms***: arteriography with selective embolization

Arteriovenous Fistula: acquired

Arteriovenous Malformation: congenital

  - ***Arteriovenous (AV) fistula***: usually iatrogenic (e.g. renal biopsy)
  - ***Arteriovenous malformation (AVM)***: congenital; cirsoid type (most common), cavernous (rare)
  - Treatment indications (as many may resolve spontaneously): HTN, cardiomegaly, congestive heart failure, severe hematuria, expanding lesion, symptomatic anemia
    - * ***AV fistula: embolization***
    - * ***Cirsoid AVM: nephrectomy (coils will migrate)***
    - * Cavernous AVM: embolization
- ***Delayed nephrectomy***: unstable patient with continued or delayed hemorrhage

| URETERAL TRAUMA |

- Most commonly ureteral trauma is iatrogenic
- Penetrating trauma is more common than blunt trauma
    - o ***Blunt trauma is more common in pediatric deceleration injuries***
        - * Spinal hyperextension leads to ureteropelvic junction disruption
- Ureteral evaluation via retrograde pyelogram, CT urogram, IVP, or direct inspection with intravenous indigo carmine or methylene blue
- **Only ~ 50% of ureteral injuries have hematuria** = need high index of suspicion
- All of the below repairs necessitate ureteral stent placement, and they are usually maintained 3-6 weeks to allow ureteral healing
- All repaired injuries need follow up in 3-6 months (earlier if flank pain) with a renogram and IVP

Ureteral Blood Supply

Superior supply is medially from aorta

Inferior supply is laterally from the iliacs

URETERAL STENT OR NEPHROSTOMY TUBE

- Indication: ***partial ureteral injury***
- Insert Foley catheter for at least 2 days to limit stent reflux
- May ultimately need a more aggressive intervention if non-healing or stricture

URETERO-URETEROSTOMY

- Indication: ***short mid-upper ureter injury*** superior to iliac bifurcation; mid-ureteral stricture
    - o Inferior to the common iliac vessels, the ureteral blood supply is more tenuous

- Concept: re-connect the ureter
- Spatulate ureteral ends to decrease stricture occurrence

TRANSURETERO-URETEROSTOMY

- Indication: ***long defect in mid-lower ureter*** with adequate proximal length to reach the contralateral ureter
- Contraindication: ipsilateral ureteral malignancy or nephrolithiasis (do not endanger the healthy ureter)
- Concept: connect the injured proximal ureter to the contralateral mid-ureter
- Ureter crosses over the aorta in the retroperitoneum, cephalad to the inferior mesenteric artery and anastomosed in a end-to-side fashion
- Optimally place stents in both ureters; however, if unable to insert both stents, then ***at least place a stent in the injured (crossed-over) ureter***

URETERO-NEOCYSTOSTOMY

- Indication: ***distal ureteral injury***
- Concept: re-implant ureter into dome of bladder
- ***In adults, ureteral re-implant may be refluxing*** (i.e. do not have to tunnel in 5:1 ratio)
- Must be tension-free, otherwise perform psoas hitch

PSOAS HITCH

- Indication: ***distal ureteral injury*** with difficulty reaching the bladder or unable to perform a tension-free repair
- Concept: mobilize and secure bladder superiorly via attachment to the psoas muscle, then tension-free ureteral re-implant
- Bladder is sutured to the psoas major muscle or psoas minor tendon
    - ***Avoid the genitofemoral nerve*** (anterior to psoas) ***and the femoral nerve*** (posterior to psoas)

Psoas Hitch Vessel Ligation / Division for Mobilization

Routinely: Contralateral (non-injured side) Superior Vesical Artery

As Needed: Contralateral (non-injured side) Inferior Vesical Artery

BOARI FLAP

- Indication: ***long mid-distal ureteral injuries,*** where psoas hitch is insufficient
- Concept: psoas hitch with bladder flap
- Flap base: 4cm minimum; apex: 3cm minimum
- Flap length: distance for tension-free anastomosis with overlap, once psoas hitch in place

ILEAL INTERPOSITION GRAFT

- Indication: ***long, severe ureteral injury*** with inability to perform any of the above procedures
- Contraindication: inflammatory bowel disease (Crohn's diease), chronic renal failure, irradiated bowel
- Graft is composed with ***distal ileum***, and interposed in the isoperistaltic position
- Check labs in follow up for hyperchloremic metabolic acidosis

AUTO-TRANSPLANT

- Indication: ***complete ureteral disruption*** with inability to perform any of the above procedures
- Contraindication: severe occlusive atherosclerosis of the iliac arteries
- Internal iliac artery preferred over external internal artery
- Renal pelvis can be directly anastomosed to the bladder

NEPHRECTOMY

- Indication: ***Inability to perform any of the above procedures or patient instability***

URETERAL LIGATION

- Indication: patients in extremis
- Ureteral ligation with percutaneous nephrostomy drainage; ureteral repair when patient is stable

TRAUMATIC URETEROPELVIC JUNCTION DISRUPTION IN PEDIATRICS

- Tx: open primary ureteropyelostomy (even if previous ureteral reimplant)

ARTERIOURETERAL FISTULA

- Surgical emergency, and potentially life threatening
- Most commonly associated with pelvic surgery, history of pelvic radiation, chronic ureteral stent, history of endovascular graft, or aortoiliac aneurysm
- Majority involve the common iliac
- Sx: ***intermittent gross hematuria*** (intermittent secondary to clot formation in fistula)
- Dx: emergent arteriography
- Tx: ***stent removal with percutaneous nephrostomy*** in addition to below
    - o Currently, ***endovascular stenting*** has become treatment of choice
        - * Common / external iliac artery is balloon dilated with stent placement if tamponade occurs secondary to the balloon
        - * Embolize (coil) the ipsilateral internal iliac artery to allow for better graft placement
    - o If unable to adequate stent or patient hemodynamically unstable, proceed with open approach
        - * Embolize the common iliac with subsequent femoral-to-femoral arterial bypass; or
        - * Arterial repair, ureteral repair / reimplantation, and omental wrap

CHAPTER 24: LOWER GENITOURINARY TRAUMA

Trauma grading scales:
http://www.trauma.org/archive/scores/ois.html

| BLADDER |

ETIOLOGY

- Blunt trauma: motor vehicle collisions, falls, assault, outlet obstruction (e.g. clot urinary retention)
- Penetrating trauma: bullet, knife, ***iatrogenic*** (most commonly secondary to obstetric and gynecologic surgery)
- Bladder injuries commonly have associated ***pelvic fractures*** (~90%)
    - Only ~10% of pelvic fractures have associated bladder injury
- Extremely rare to have concurrent upper and lower urinary tract traumatic injuries (< 0.5%)
- Spontaneous augmented bladder perforation: most commonly from ischemic necrosis (not mucus plugging)

Pediatric Bladder

Pediatric bladders are abdominal organs and rupture at lower capacities

DIAGNOSIS

- Sx: ***gross hematuria***, suprapubic tenderness, inability to void, orthopedic pain (i.e. fractures), abdominal guarding and distention, ileus, peritonitis
- Insert a Foley catheter if bladder rupture is suspected
  - ***Retrograde urethrogram if blood at meatus or difficult Foley***
    - Up to ~1/3 of bladder injuries may have associated urethral injury
- Vaginal laceration or vaginal bleeding: rule out concurrent bladder neck injury
- If bladder injury during a hysterectomy, evaluate the ureters for injury as well
- Lab: azotemia (peritoneal absorption of urea)
  - Creatinine level of peritoneal or retroperitoneal fluid should be nearly the same as the serum level.
    - Fluid creatinine > serum creatinine = urinary tract leakage

IMAGING

- Cystogram or CT cystogram: retrograde contrast instillation with subsequent imaging
  - Indications: (1) blunt trauma resulting in a pelvic fracture with gross hematuria (~1/3 will have bladder rupture); (2) penetrating trauma with gross or microscopic hematuria
    - Consider if blunt trauma resulting in gross hematuria without a pelvic injury or if blunt trauma resulting in pelvic fracture with microscopic hematuria
  - ***Antegrade filling of the bladder with IV contrast is not an acceptable method to evaluate for bladder injury!***

Cystogram

Instill ≥ 350 cc of contrast for adequate study

(Stop instillation immediately if pain upon filling or extravasation noted)

- Plain cystogram films: scout, full instillation, post-drainage films; may use regular strength cystogram contrast (30%)
- CT cystogram: must dilute contrast (2-4%) to avoid artifact
- ***Bladder contusion***: urothelium ± detrusor injury without extravasation on cystogram
- ***Extraperitoneal injury***: contrast within the retroperitoneum; however, may extend into the thigh, scrotum, or anterior abdominal wall; flame-like appearance
- ***Intraperitoneal injury***: contrast lines the small bowel loops and/or line the paracolic gutter
    - Bladder dome rupture secondary to rapid blunt compression of a full bladder

Pelvic Hematoma

Bladder compression appears as a teardrop deformity on cystogram

TREATMENT

- Extraperitoneal injury: ***catheter drainage*** for ~ 14 days
    - Consider repeat cystogram prior catheter removal; if continued leak, maintain the catheter vs. surgical repair
    - ***Cystorrhaphy*** indications: if going to the operating room for other injuries; bone fragment within bladder; open pelvic fracture; vaginal or rectal injury

Anterior injuries

- ***Perineal butterfly hematoma***: Buck's fascial injury resulting in a hematoma contained by Colles fascia; may include scrotal ecchymosis
- Female anterior urethral injury: vulvar hematoma / edema, vaginal bleeding

Categories

- Contusion, partial rupture, or complete rupture

IMAGING

Posterior injuries

- Pubic or sacroiliac joint diastasis, anterior pelvic ring fracture, and straddle fractures (multiple pubic rami fractures)
- Retrograde pyelogram: ***"Pie-in-the-sky" bladder***
    - Posterior urethral injury with a pelvic hematoma results in cephalad displacement of the bladder

Retrograde Pyelogram (RUG)

Retrograde contrast instillation of ~ 25 cc

(Cystoscopy is preferred in females)

URETHRAL BLUNT TRAUMA CLASSIFICATION

Grade	Description	RUG Findings	Incidence
1	Membranous urethral stretch, but intact (puboprostatic ligament rupture)	No extravasation	10-15% posterior injuries
2	Membranous urethral injury proximal (above) to the urogenital diaphragm	Retroperitoneal contrast extravasation	10-15% posterior injuries
3	Membranous urethral injury proximal and distal to the urogenital diaphragm (perineal membrane)	Perineal ± retroperitoneal contrast extravasation	70-80% posterior injuries
4	Bladder neck injury extending to the urethra	May be seen better on a VCUG	Rare
4a	Extraperitoneal bladder rupture with pseudo-urethral injury	May be seen better on cystogram	Not a urethral injury
5	Anterior urethral injury only (common with straddle or perineal injury)	Bulbous or pendulous urethral extravasation	10% of all urethral injuries

TREATMENT

- See Urethral Disease Chapter for further details on urethroplasty
- Men: attempt endoscopic ***primary realignment with delayed urethroplasty*** as necessary
  - o Realignment sequence: (1) Foley insertion (2) flexible cystoscopy (3) operating room – retrograde or antegrade (4) suprapubic cystostomy
    - * Maintain Foley for 6 weeks and check pericatheter RUG
  - o Immediate urethroplasty in men have higher rates of incontinence, erectile dysfunction, and strictures
  - o Posterior urethral injury: majority will heal with primary

realignment (< 10% will require ***perineal anastomotic urethroplasty*** to realign) and ~ 50% will heal without stricture disease

 - * Concern for urinary incontinence, recurrent stricture, and erectile dysfunction

- Women: immediate urethroplasty with vaginal laceration repair
  - o Delayed urethroplasty in females have higher rates of urethrovaginal fistulas and urethral strictures
- ***If unable to place a urethral catheter, insert a suprapubic cystostomy (SPT)***
  - o Antegrade primary alignment may be attempted if retrograde catheterization was unsuccessful
  - o Posterior urethral injury: SPT alone will result in stricture disease in nearly all patients
  - o If SPT and Foley, remove the Foley 1st and maintain the SPT for 1-2 weeks because of potential posterior urethral stenosis
- Penetrating urethral injury: immediate urethroplasty
- Bladder neck injury: immediate repair
- Concomitant rectal injury: immediate repair and fecal diversion

| PENIS |

PENILE FRACTURE

Etiology

- Tunica albuginea rupture or tear from buckling of an erect penis, usually during intercourse
  - o ***Taqaandan***: "to click"; Middle Eastern (particularly Iran) practice of bending an erect penis to achieve rapid detumescence
- Tunica albuginea is thinnest ***ventrolaterally***, and most susceptible to injury

DIAGNOSIS

- May hear popping sound at time of injury
- ***Eggplant Deformity***: penile shaft ecchymosis alone secondary to hematoma contained by Buck's fascia
    - If Buck's fascia is ruptured, the hematoma will be contained within the scrotum and perineum by Colles fascia (Butterfly Hematoma)
- ***Flexible cystoscopy*** is recommended in operating room prior to tunica repair to rule out concomitant urethral injury, which is seen in 10-20% of penile fractures
    - ***RUG***: delays repair and may be inaccurate; however, it is an option
- ***MRI***: indicated in atypical presentations; clearly delineates tunica albuginea rupture

Dorsal Penile Vessel Rupture

Mimics penile fracture without tunica albuginea rupture

Treatment

- Immediate repair via penile degloving with tunica albuginea closure, and urethral repair if injury present
- If uncircumcised, consider circumcision as the degloving has risk of prepuce ischemia
- Side effects: erectile dysfunction, Peyronie's disease, urethral stricture
    - The earlier repair the lower incidence of side effects
- If dorsal penile vessel rupture, may consider conservative management or vessel ligation

PENETRATING PENILE INJURIES

- Most common etiology is genital gunshot wounds
- RUG: 25-40% have urethral injury
- Tx: immediate exploration, debridement, and penile repair ± immediate urethroplasty if urethral injury present

PENILE AMPUTATION

- Usually mentally-ill patients performing self-mutilation
- Clean penis, wrap in saline soaked gauze, place within a plastic bag, place this bag within a second plastic bag containing ice slush
- Tx: macroscopic vs. microvascular reconstruction have similar erectile function results
    - ***Macroscopic***: reanastomosis of the corpora cavernosum and corpora spongiosum ± medical leech therapy to increase venous outflow (essentially a free graft)
    - ***Microvascular***: macroscopic reanastomosis with microvascular reconstruction of dorsal arteries, veins, and nerves
    - Increased sensation and decreased skin ischemia
    - ***If penis is unavailable for reconstruction***, formalize amputation. Need 2cm base to avoid perineal urethrostomy
    - Side effects: erectile dysfunction (~50%), strictures, neuropathy, skin necrosis, penile ischemia with need for formalized amputation

PENILE BITES

- Most common etiology is dog bites
- Polymicrobial infections: most commonly ***Pasteurella multocida, Staphylococcus aureus, and anaerobic bacteria***
- Tx: wound irrigation, debridement, immediate primary closure (dog bites) or healing by secondary intention (human bites)
    - Antibiotic is imperative: ***amoxicillin-clavulanic acid***; clindamycin + ciprofloxacin; clindamycin + trimethoprim-sulfamethoxazole; or daily rocephin
    - Tetanus and/or rabies vaccinations as indicated

PENILE ZIPPER INJURY

- Usually prepubertal boys
- Penile block with single attempt to unzip the zipper
- If unsuccessful, cut zipper slider then the zipper teeth with a wire cutters

- Immediate closure of skin laceration, and consideration for circumcision as necessary

PENILE SKIN LOSS

- Remove all shaft skin distal to injury, and place ***non-meshed,*** split thickness skin graft (usually await 5-7 days to allow bacterial decontamination)
    - Remaining distal skin will result in circumferential lymphedema, and may lead to ischemia
    - Meshed grafts contract (do not used on the penis, ok for scrotum)
    - Penile shaft grafts result in loss of sensation; however, the glans still has normal sensation

| SCROTUM |

- ***Scrotal skin loss ≤ 60% is usually amenable to primary closure***
- If > 60%, ***meshed*** split-thickness skin grafts are usually required
- Thigh pouches may be used to protect the testicles from infection and injury

Preferred Skin Grafts

Penis: non-meshed, split thickness skin graft

Scrotum: meshed, split thickness skin graft

| TESTICLE |

ETIOLOGY

- Blunt injury (75%): assault, sports injury, motor vehicle injury
- Penetrating injury (25%): gunshot, impalement
  - o More common to have bilateral injury (up to 30%)

Penetrating Testicular Injury

Imperative to evaluate femoral vessels for injury

DIAGNOSIS

- Sx: pain, nausea, vomiting, hematoma, hydrocele, hematocele
- ***Ultrasound***: assess the integrity of tunica albuginea, presence of hematoma, and normal homogenous parenchyma
  - o If equivocal → immediate exploration
- Injury types: contusion, hematoma, rupture of tunica albuginea, testicular torsion

TREATMENT

- Contusion: conservative treatment
- Hematoma: conservative treatment; if large hematoma, drain to decrease recovery time, infection, testicular atrophy
- Hematocele: immediate exploration, as a large majority will have undiagnosed testicular rupture
- Rupture: immediate exploration; debride necrotic / extruded seminiferous tubules and close tunica albuginea
  - o Tunica vaginalis may be used as a graft if inadequate tunica albuginea
  - o ~ 90% testicular salvage if repaired ≤ 3 days in blunt trauma
  - o Conservative management may lead to theoretical anti-sperm antibodies

Testicular Rupture

If ≥ 50% of the testicle is salvageable, attempt repair

- Torsion: ipsilateral orchidopexy if viable (orchiectomy if not viable), and contralateral orchidopexy
- Penetrating injury: immediate exploration
    - Vas deferens injury → permanent suture ligation with delayed vasoepididymostomy as necessary
- Children with one testicle may play contact sports; however, he needs to take appropriate precautions (e.g. genital cup)

CHAPTER 25: SEXUAL DYSFUNCTION

| PENILE ANATOMY AND PHYSIOLOGY |

ANATOMY

- Corpora cavernosa are individually encased by the tunica albuginea, and both corpora cavernosa and spongiosum are wrapped together by ***Buck's fascia***.
    - o Bucks fascia is surrounded by ***Dartos fascia***
- **Arterial supply**: common iliac → internal iliac → posterior division of the internal iliac → internal pudendal → ***dorsal penile artery*** (located beneath Buck's fascia) and ***cavernosal artery*** (aka: deep penile artery; located within the corpora cavernosa)
    - o The dorsal neurovascular bundle runs near the midline with the dorsal penile artery beneath Buck's fascia; this also includes the ***deep dorsal vein*** and ***dorsal nerve of the penis*** from the pudendal nerve (penile sensation)

PHYSIOLOGY

- ***Erection***: penile tumescence
    - o ***Parasympathetic*** response via **S2-4** nerve roots (***cavernosal nerves***)
        - * Injury to the sacral nerve roots may occur in prostatectomy, abdominal perineal resection
    - o ***Veno-occlusive physiology***: brisk arterial inflow via smooth muscle relaxation compresses the venous outflow, resulting in

  trapped blood within the corpora cavernosa

  - Main pathway for erections: Sexual arousal leads to increased ***nitric oxide*** levels, which along with guanylate cyclase converts ***GTP*** (cyclic guanosine triphosphate) ***to cGMP*** (cyclic guanosine monophosphate). This results in decreased intracavernosal calcium, which ultimately leads to smooth muscle relaxation
    - Negative feedback: ***phosphodiesterases type 5*** (PDE-5) normally degrades cGMP (inhibition of this negative feedback is the main pathway for oral erectile dysfunction medications)
  - Accessory pathway for erections: smooth muscle relaxation via increased ***cAMP*** (cyclic adenosine monophosphate)
    - cAMP is degraded by phosphodiesterases; however, not by type 5.
    - Intraurethral/intracavernosal ***prostaglandin E1 (alprostadil)*** increases cAMP production; ***papaverine*** is a non-specific PDE inhibitor that increases both cGMP and cAMP
      - Alprostadil is the only FDA approved intracavernosal injection for erectile dysfunction
  - Indirect pathway for erections: ***alpha adrenergic receptor blockade*** results in cavernosal smooth muscle contractions relaxation
    - Alpha-adrenergic stimulation usually causes contraction of the cavernosal smooth muscle cells; blockade results in muscle relaxation and arterial dilation
    - ***Phentolamine*** is non-specific alpha-blocker commonly used in conjunction with papaverine and alprostadil.
- ***Emission***: sperm and semen exit ejaculatory ducts into the urethra
  - ***Sympathetic*** response via **T10-L2** nerve roots (***hypogastric nerves***)
    - Injury to thoracolumbar nerve roots may occur in aortic bypass, aortic aneurysm repair, and ***retroperitoneal lymph node dissection (RPLND)***
- ***Ejaculation***: forceful ejection of semen/sperm from the urethra
  - ***Somatic*** response via the ***pudendal nerve***

Smooth Muscle Relaxation for Erection

Main path: GTP + nitric oxide + guanylate cyclase → ***cGMP*** decreased intracavernosal calcium

Accessory path: increased ***cAMP*** decreased intracavernosal calcium

SEXUAL DYSFUNCTIONS

Note: *these categories may change with the upcoming DSM-V*

1. **Sexual interest/desire dysfunctions**
    - a. Hypoactive sexual desire disorder
        - i. NOTE: oral contraceptive pills decrease libido by increasing sex hormone binding globulin, thus lowering free testosterone
    - b. Sexual aversion disorder
2. **Sexual arousal dysfunctions**

    Men

    - a. Erectile dysfunction
    - b. Premature ejaculation

    Women

    - c. Subjective sexual arousal dysfunction
    - d. Genital sexual arousal dysfunction (e.g. decreased lubrication, vulvar swelling, reduced sensation)
        - i. If post-menopausal vaginal atrophy, treat with ***vaginal estrogen cream*** or oral ***ospemifene*** (selective estrogen receptor modulator)
            1. Contraindications: endometrial or breast cancer
            2. Side effects: flushing, headache, endometrial thickening
    - e. Combined subjective and genital arousal dysfunction
    - f. Persistent genital arousal dysfunction (e.g. spontaneous and

undesired genital arousal that is not relieved with orgasm)

3. **Orgasmic dysfunction**

Men

  a. Delayed ejaculation
  b. Orgasmic dysfunction (e.g. inability to achieve orgasm)
  c. Anejaculation

Women

  d. Delayed or absent orgasm

4. **Sexual pain dysfunction** (women)
  e. Dyspareunia – painful intercourse
  f. Vaginismus – painful vaginal spasms upon contact or insertion

| ERECTILE DYSFUNCTION |

- Inability to achieve and maintain an erect penis satisfactory for sexual intercourse
- Present in up to 50% men > 40 years of age

ETIOLOGY

- Organic etiologies: 90%
  - o **Arteriogenic** (most common)
    - * May be first and early sign of underlying ***cardiovascular disease***
    - * Associated with diabetes mellitus, trauma, pelvic surgery (e.g. prostatectomy, RPLND, low-anterior resection, aortic surgery)
  - o **Veno-occlusive (aka: *venous leak*)**
    - * Associated with Peyronie's disease, diabetes mellitus, pelvic surgery

- o **Neurogenic**
  - * Associated with diabetes mellitus, alcoholism, multiple sclerosis, spinal cord injury, nerve injury during pelvic surgery
- o **Hormonal**
  - * Associated with hypothyroidism, hyperthyroidism, hypogonadism, hyperprolactinemia
- o **Medication side effect**
  - * Selective serotonin reuptake inhibitor, beta-blockers, antidepressants, antipsychotics, diuretics, LHRH agonist/antagonists, pain medications, H2-blockers

- Psychogenic (only 10%)
  - o Usually younger men; will have nocturnal erections
  - o Tx: psychotherapy, sexual therapy

WORKUP

- Lipid panel (related to cardiovascular disease)
- Fasting blood sugar or hemoglobin A1c (related to diabetes)
- Testosterone panel (LH, testosterone, sex-hormone binding globulin)
- Palpate / Doppler peripheral pulses (related to atherosclerosis)
- Neurologic exam to evaluate lumbosacral nerve roots

Penile Doppler Ultrasound

- Normal peak cavernosal artery systolic velocity is ***≥ 35 cm/second***
  - o Need at least 25 cm/sec to achieve an erection
  - o < 25 cm/sec = severe arterial disease
- Normal peak cavernosal artery end-diastolic during an erection is ***< 5 cm/sec***
  - o ***Venous leak:*** > 5 cm/second peak end-diastolic
    - * PDE5 inhibitors have poor results in patients with venous leak; strongly consider penile prosthesis or vacuum device

Rigiscan

- Device to measure nocturnal tumescence
- Normally 2-3 erections/night lasting ~ 15 minutes with 50-60% rigidity

Cavernosometry

- Measurement of intracavernosal vascular pressure
- ***Presence*** of venous leak

Cavernosography

- Intracavernosal, contrast-injected, radiographic imaging of the corpus cavernosum
- ***Location*** of venous leak and anatomic abnormalities

International Index of Erectile Function (IIEF) Questionnaire: 15 questions that addresses 5 domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction)

- Erectile Function Domain Scoring
    - 26-30: No ED
    - 22-25: Mild ED
    - 17-21: Mild-moderate ED
    - 11-16: Moderate ED
    - 6-10: Severe ED

Sexual Health Inventory for Men (SHIM): 5-item questionnaire derived from the IIEF

- 22-25: No ED
- 17-21: Mild ED
- 12-16: Mild-moderate ED
- 8-11: Moderate ED
- 5-7: Severe ED

TREATMENT

PDE-5 INHIBITORS

- Inhibit cGMP degradation (still requires sexual stimulation to increase penile nitric oxide levels and induce the cascade for erection)

- 60-80% of patients will achieve adequate erections
- Class side effects: headache, rhinitis, headache, dyspepsia (sphincter relaxation), non-arteritic anterior ischemic optic neuropathy (NAION), visual disturbances (bluish hue), rarely priapism
    - ***NAION***: significant decrease in visual field and acuity
        - * Highest risk: HTN, DM, hyperlipidemia, > 50 years old, cardiovascular disease, or smoker
- Contraindication***: concomitant nitrates, history of NAION***
    - Do not take PDE5 inhibitors within 4 hours of an alpha blocker (e.g. tamsulosin) to avoid potential orthostatic hypotension
- ***Sildenafil*** (25, 50, 100 mg)
    - Peaks within 1 hour
    - T ½: 4 hours
    - Side effect: ***bluish visual hue (PDE-6 inhibition)*** – will wear off after 4-5 half-lives
    - Do not take within 2 hours of a fatty meal (decreased effectiveness)

Sildenafil and Pulmonary Hypertension

Sildenafil is indicted for pulmonary hypertension; if it leads to priapism, dose reduction usually results in detumescence

- ***Vardenafil*** (2.5, 5,10, 20 mg)
    - Also 10mg oral dissolve tablet (Staxyn®)
    - Peaks within 1 hour
    - Side effect: ***bluish visual hue (PDE-6 inhibition)*** – will wear off after 4-5 half-lives
    - T ½: 4 hours
    - Does not take within 2 hours of a fatty meal – decreased effectiveness

- *Tadalafil* (2.5, 5, 10, 20 mg)
  - T ½: 18 hours
  - Only PDE5 with daily dose formula; and only PDE5 indicated for BPH
  - Side effect: ***myalgias (PDE-11a inhibition)***

VACUUM ERECTION DEVICE (VED)

- The VED draws blood into the penis by creating a vacuum, and then a constriction ring is placed at the base of the penis to maintain the erection for intercourse.
- Works well for ***venous leak***
- Good success rate, but poor long term satisfaction

PROSTAGLANDIN E1

- ***Alprostadil (PGE-1)*** – **Intracavernosal Injection**
  - Activates cAMP directed smooth muscle relaxation
  - Erection without sexual stimulation
  - Efficacy: 60-80%
  - Alternate sides and sites for injection
  - Side effects: penile pain, fibrosis, bleeding, priapism
  - Contraindication: penile prosthesis, predisposition for priapism (sickle cell disease or trait, multiple myeloma, leukemia), Peyronie's disease
  - NOTE: Alprostadil, Papaverine, and Phentolamine combination (TriMix) is not currently FDA approved
- ***Alprostadil (PGE-1)*** - **Intraurethral Pellets**
  - Activates cAMP directed smooth muscle relaxation
  - Efficacy: 30-40%
  - May be used in conjunction with a VED
  - Side effects: Urethral burning, penile pain, urethral bleeding, priapism
  - Contraindications: predisposition for priapism (sickle cell disease or trait, thrombocythemia, polycythemia, multiple

myeloma), DVT, intercourse with a pregnant woman unless a condom is used

Erectile Dysfunction and Pelvic Injuries

Neurogenic injuries respond better than arterial injuries to PGE-1 and PDE-5 inhibitors

PENILE PROSTHESIS

- ***Malleable/semi-rigid***
  - Pro: good for patients with poor dexterity
  - Con: rigidity is present at all times, and may be difficult to conceal
- ***Inflatable penile prosthesis (IPP)***
  - 2-piece and 3-piece available (3-piece is gold standard)
  - Complications: infection (< 1-2%; diabetics 2-3%; spinal cord injury 30%), erosion, malfunction (5% at 5 years), penile shortening 1-2cm, auto-inflation
    - Acute infection: staphylococcus aureus
    - Delayed infection: staphylococcus epidermidis
  - If infected prosthesis, may offer salvage procedure with washout (~80% success rate); goal is to clear bacteria and ***biofilm***
    - Removal of entire prosthesis; washout entire area with antibiotic regimen; regimens are variable, but a common example is:
      - Vancomycin-gentamicin (bactericidal)
      - Hydrogen peroxide (anaerobic bacteria)
      - Betadine (bactericidal)
      - Pressure washing (biofilm removal)
      - Repeat in reverse order
  - ***Supersonic transport (ST) deformity***: distal penis/glans has a ventral chordee secondary to under-sizing of IPP cylinders

        - Tx: dorsal subcoronal plication or IPP cylinder replacement
    - If proximal corporal perforation with crossover, re-dilate and continue procedure once in correct corporal body
        - May also place non-absorbable "suture sling" through the rear tip extender to maintain the cylinder position during post-operative healing
    - If distal perforation with a urethral injury, abandon the implantation and retry in the future. Maintain Foley catheter 3-5 days.
        - If one side is already inserted, may leave that side in place with pump/reservoir. Some patients may find, single cylinder acceptable for intercourse, and avoid second procedure.

IPP with Concurrent Procedures

Perform IPP first, close all IPP incisions, and then proceed with indicted procedures (e.g. circumcision, herniorrhaphy)

REVASCULARIZATION

- Pelvic trauma with arterial injuries may benefit from revascularization
- ***Internal Pudendal Artery*** is the key arterial supply for erections, and may be injured with inferior pubic rami fractures
- Most reconstructions utilize the ***inferior epigastric artery***
- ~ 50% long term success rate
    - Approximately half will need pharmacologic induced erections
    - Patients < 30 years old, non-smokers, and without venous leak have the greatest success
- Complications: thrombosis, ***glans hyperemia*** (dorsal vein arterialization), priapism

TESTOSTERONE REPLACEMENT THERAPY (TRT)

- Formulations: topical gels, intramuscular, buccal, transdermal, pellet implant
- Indications: hypergonadotropic hypogonadism (primary), hypogonadotropic hypogonadism (secondary)
  - May be beneficial in hypogonadal men with erectile dysfunction
- Contraindications: Men with breast cancer or suspected prostate cancer
- Side effects: worsening of BPH, PSA elevation, azoospermia (not good choice if desiring pregnancy), edema, sleep apnea, hypoglycemia, virilization of children, hepatic adenomas (intramuscular application), hepatotoxicity, gynecomastia
- Lab: Monitor PSA, serum testosterone, hemoglobin/hematocrit (polycythemia), liver function tests (hepatitis, hepatic adenomas), and lipid panel (hyperlipidemia)
  - If hematocrit > 52%, hold testosterone, consider phlebotomy
  - Monitor symptoms for sleep apnea, edema (sodium retention)
  - ***Stop therapy and biopsy for any of the following:***
    - PSA increase of > 1.4 ng/mL
    - Increased PSA velocity (e.g. ≥ 0.35 or 0.75 ng/mL/year)
    - Abnormal DRE

PENILE REHABILITATION

- Commonly used if erectile dysfunction post-prostatectomy
- Optimal regimen is unknown, but options include: VED, PDE-5 inhibitors, Alprostadil
- Goal: preserve the cavernosal architecture, and prevent fibrosis (smooth muscle → collagen); this allows for cavernosal nerve injury to recover
- Allow at least ***1 year*** for nerve recovery prior penile prosthesis

YOHIMBINE

- Central acting alpha-2 adrenergic receptor antagonist
- Studies have shown it to be ineffective

| PRIAPISM |

- Persistent erection for > 4 hours in the absence of sexual excitement
    - Ischemic vs. non-ischemic

ETIOLOGY

ISCHEMIC (LOW FLOW)

- Sickle cell disease and other hemoglobinopathies
- Erectile dysfunction pharmacotherapies
    - Much more common with intracavernosal injections (e.g. prostaglandin E1) than oral PDE5 inhibitors (rare)
- Antihypertensives (e.g. hydralazine, prazosin)
- Antipsychotics (e.g. risperidone)
- Antidepressants (e.g. trazodone)
- Alcohol, Cocaine
- Neoplastic disease (thrombophilic)
- Leukemia
- Polycythemia
- Parenteral nutrition with high lipid concentration
- Hemodialysis
- Heparin treatment
- Anesthesia (general, regional)

NON-ISCHEMIC (HIGH FLOW)

- Trauma
- Straddle injury
- Neurologic conditions
- Laceration from intracavernosal injection needle
- Penile revascularization surgery
- Acute spinal cord injury (usually self-limited to < 24 hours)

MOST COMMON ETIOLOGIES OF PRIAPISM

Pediatrics	Adults
Sickle cell	Idiopathic
Leukemia	Medication
Idiopathic	Sickle cell
Trauma	Neoplasia
	Trauma
	Neurologic disease

PRIAPISM PRESENTING SYMPTOMS COMPARISON

Symptoms	Ischemic	Non-ischemic
Etiology	Veno-occlusive	Arterial inflow
Tenderness / Pain	Yes	No
Tumescence	Rigid	Fullness
Cavernosal arterial flow	Minimal / none	Normal / high
Blood aspirate	Dark	Bright red
Compartment syndrome	Yes	No
Emergency	Yes	No
Erectile dysfunction secondary to priapism	Variable (30-90%)	Infrequent

The penile glans is usually detumesced in ischemic and non-ischemic priapism.

STUTTERING PRIAPISM

- Recurrent ischemic erection lasting < 4 hours; however, may occasionally last > 4 hours and jeopardize penile tissue

- Approximately 25% of these patients will have resultant erectile dysfunction
- Most commonly seen in ***sickle cell disease***

WORKUP

- Usually a clinical diagnosis, and further work up is unnecessary
- Corpora cavernosal blood gas may be helpful to differentiate between ischemic and non-ischemic priapism

CAVERNOUS BLOOD GAS FINDINGS*

	pH	pCO2	pO2	Presentation
Ischemic	7.25	60	30	Acidosis
Flaccid penis (normal)	7.35	50	40	Mixed venous blood
Non-ischemic	7.4	40	90	Arterial blood

**Approximate values*

- **Color Duplex Ultrasonography**
    - o ***Ischemic***: low or no cavernosal arterial flow
    - o ***Non-ischemic***: high or normal cavernosal arterial flow
- Other imaging options include: penile arteriography, scintigraphy, cavernosography

TREATMENT

ISCHEMIC PRIAPISM

- Treat underlying condition
    - o Sickle cell: aggressive hydration, 100% oxygen, pain control
- Aspiration with irrigation
    - o ~ 1/3 resolution
- Intracavernosal Phenylephrine injection

  - o Alpha adrenergic agonist
  - o 100-500 mcg / 5 minutes until detumescence; 1,000-1,500 mcg maximum cumulative dose
    - * Lower doses (100-200mcg) for patients with cardiovascular disease
  - o Continuously monitor blood pressure and EKG
  - o Up to ~ 75% resolution
- Distal shunt
  - o The therapeutic goal is to create a ***cavernoglanular fistula***
  - o ***Winter***: percutaneous biopsy needle through penile glans into the distal corpora cavernosa
  - o ***Ebbehoj***: scalpel insertion through penile glans into the distal corpora cavernosa
  - o ***Al-Ghorab***: excision of distal corpora cavernosal tunica albuginea (most effective distal shunt, but requires going to the operating room)
- Proximal shunt
  - o ***Quackels***: proximal fistula created between corpora cavernosum and spongiosum
  - o ***Grayhack***: proximal fistula created between the saphenous vein anastomosed to the corpora cavernosum
    - * Risk: pulmonary embolism
  - o ***Barry***: proximal fistula created with the penile dorsal vein anastomosed to the corpora cavernosum
- Penile Prosthesis
  - o Obliterates the corpora cavernosal bodies, thus eliminates the priapism
  - o Early prosthesis avoids post-priapism intense cavernosal fibrosis

Note: *pseudoephedrine and terbutaline have been shown to be ineffective.*

NON-ISCHEMIC PRIAPISM

- Conservative management / observation
  - ~ 2/3 will resolve spontaneously
- Selective arterial embolization
  - Utilization of nonpermanent embolization material results in less erectile dysfunction compared to permanent materials (5% vs. 40%)
  - Risk: perineal abscess
  - ~ 75% resolution
- Penile exploration with ligation
  - High erectile dysfunction rate
  - ~ 2/3 resolution

STUTTERING PRIAPISM

- The therapeutic goal is medical treatment to reduce or eliminate recurrent priapism
- **Hormonal manipulation** is the most successful treatment; only use if postpubertal
  - GnRH Agonists (e.g. ***Leuprolide***)
    - * Initially may need concurrent anti-androgen to prevent increased risk of priapism associated with early testosterone surge
  - Androgen receptor antagonists (e.g. ***Bicalutamide, Flutamide***)
  - Goal: serum testosterone 10% below normal physiologic levels
- ***Tadalafil*** (PDE5 inhibitor) has a paradoxical effect by regulating cGMP breakdown, thus reducing priapism recurrence
- Self-injected, intracavernosal phenylephrine injection
- If lasts > 4 hours, start with ischemic priapism treatments above

| PEYRONIE'S DISEASE |

- ***Penile tunica albuginea plaque*** resulting in pain and erection curvature
    - Likely secondary to trauma or microvascular injury
- **Phase 1: Acute inflammation**
    - Soft plaque
    - ***Painful erections***
    - Worsening curvature
- **Phase 2: Fibrosis / stabilization** (usually within 1 year)
    - Hardening / calcifying plaque
    - Non-painful erections
    - Stabilized curvature
- Painful erections resolves spontaneous in vast majority (~90%)
- Associated with ***Dupuytren's contracture*** and ***plantar fasciitis***

WORKUP

- Plaque is usually palpable
- Measure penile-stretch length and degree of curvature to help guide treatment options
- Examination of erection is required
- Ultrasound is unreliable for Peyronie's' disease; however, may be needed to evaluate concomitant erectile dysfunction

TREATMENT

Phase 1: ***Conservative treatment until resolution of painful erections***

- Potassium para-aminobenzoate (Potaba)
- Intralesional verapamil
- Intralesional clostridial collagenase histolyticum (FDA approval pending)
- Topical 15% verapamil
- Colchicine

- Traction device
- Vacuum device
- Spontaneous resolution in up to ~10%

Phase 2: ***Surgical treatment usually needed once the plaque has stabilized for at least 3 months*** (usually after 1 year, most plaques will be stable)

- ***Penile shortening procedures***: Nesbit procedure; 16-dot plication
    - < 60° curvature; normal penile length
- ***Penile lengthening procedures***: tunica albuginea graft procedures
    - > 60° curvature; shortened penis
    - Good erectile function prior procedure
    - Complications: increased erectile dysfunction and penile numbness secondary to neurovascular bundle mobilization
- ***Penile prosthesis***: allows for modeling and resultant penile straightening
    - Indicated for patients with associated erectile dysfunction that do not respond to phosphodiesterase-5 inhibitors
    - ***Modeling***: (1) inflate IPP to maximum rigidity and place a rubber shod to protect the pump (2) bend penis against curvature and hold for 90 seconds (3) remove clamps and pump addition fluid to maximum rigidity (4) repeat above steps (5) check result
        - Goal is < 30° curvature (may repeat above steps to achieve goal as necessary)
    - If unable to adequately model plaque with prosthesis, consider graft with prosthesis

| PREMATURE EJACULATION (PE) |

- Ejaculation prior to the desire of either partner
- Most common male sexual dysfunction
- Primary (lifelong) vs. secondary (acquired) vs. situational
    - Secondary PE is commonly associated with erectile dysfunction, which should be addressed first

      - * Other etiologies: hyperthyroid (increased sympathetics), anxiety

- ***Intravaginal ejaculation latency time (IELT)***: time from vaginal intromission to intravaginal ejaculation
  - o ~ 6-7 minutes is average IELT
- Tx options:
  - o Behavioral techniques such as the start-stop technique
  - o ***EMLA cream (Lidocaine 2.5% and prilocaine 2.5%)***: topical anesthetic applied to the penis to decrease sensation
  - o ***Paroxetine / Sertraline (Selective Serotonin Reuptake Inhibitors)*** utilizes common class side effect – delayed climax
    - * May lead to anorgasmia, decreased libido, erectile dysfunction
  - o ***Clomipramine (tricyclic antidepressants)***: more effective than SSRIs; however, increased undesired side effects
  - o ***Sildenafil / Tadalafil (PDE-5 inhibitors)***: consider in patients with concurrent erectile dysfunction
  - o ***Tramadol (synthetic opioid analgesic)***: weak µ-opioid effect; however, inhibits norepinephrine and serotonin reuptake as well

| HEMATOSPERMIA |

- Blood within semen
- ***Usually benign and self-limiting***
- Etiologies: prostate biopsy (up to 3 months post-biopsy), trauma, infection, inflammation, GU tumor, prostatic calculi or cysts, uncontrolled hypertension, vascular malformations
- Workup: usually reassurance, particularly in younger males. May consider the following, depending on the presentation:
  - o DRE / PSA
  - o Urine analysis with culture
  - o Sexual transmitted disease testing

  - Transrectal ultrasound
  - Cystoscopy

| COLD GLANS SYNDROME |

- Patients complain of the glans penis having a cold sensation, which may also be identified on thermal imaging
- Tx: ***Alprostadil (PGE-1) intraurethral pellet***

CHAPTER 26: INFERTILITY

DEFINITIONS

- **Infertility**: ≥ 1 year of unprotected intercourse with the inability to conceive
  - 10-15% of couples affected in the USA
  - Etiology: male 20%, female 40-50%, both 30-40%
- **Primary infertility**: patient has never been able to conceive
- **Secondary infertility**: patient has previous ability to conceive, but unable now
- **Aspermia**: absence of any ejaculate
- **Azoospermia**: absence of sperm in ejaculate
- **Oligospermia**: low sperm count in ejaculate (< 15 million sperm / mL)
- **Asthenospermia**: decreased sperm motility
- **Teratospermia**: abnormal sperm morphology
- **Oligoasthenoteratospermia**: abnormalities in sperm count, motility and morphology

ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

- **IUI:** intrauterine insemination
  - Semen is inserted into the uterus (requires > 5 million motile sperm count)
  - Indication: cervical-factor infertility, isolated oligospermia, obstruction
  - Advantage: circumvents the cervical mucous barrier
- **IVF:** in vitro fertilization

  - Ovum is fertilized in the laboratory, then placed into mother's uterus
  - Slight increased risk of congenital malformations; sex chromosome abnormality (0.2%)
  - Pregnancy rates up to 40-50% depending on female's age
- **ICSI**: intracytoplasmic sperm injection
  - Injection of a single sperm into an ovum
  - Pregnancy rates 30-40%; Delivery rates 25-30%
  - Advantage: circumvents the need for the acrosomal reaction for sperm penetration of the oocyte
  - Slight increased risk of congenital malformations; sex chromosome abnormality (~1%); twins (~ 30%); triplets (< 5%)
- ICSI and IVF have very poor results in women > 40 years old; use donor ova
- **Frozen donor sperm**: may re-screen donors at later date (prior to use) for HIV and other diseases. Lower per cycle pregnancy rate than fresh sperm; however, similar cumulative pregnancy rates.

SPERM RETRIEVAL TECHNIQUES

- **Testicular procedures**
  - **TESE**: testicular sperm extraction (open vs. microscopic)
  - **TESA**: testicular sperm aspiration (percutaneous)
  - **TEFNA**: testicular fine-needle aspiration (percutaneous)
- **Epididymal procedures**
  - **MESA**: microsurgical epididymal sperm aspiration
  - **PESA**: percutaneous epididymal sperm aspiration
- **Spinal Cord Injury patients** (anejaculatory patients)
  - **PVS**: penile vibratory stimulation
    - Ejaculatory reflex (T10-S4) must be intact (i.e. injury above T10)
    - Beware of ***autonomic dysreflexia*** if injury ***above T6***
    - Usually antegrade ejaculations
  - **EEJ**: electroejaculation

  - Indicated for all spinal cord injury levels; however, due to invasiveness of procedure and potential anesthetic requirement, it is usually consider second line therapy to PVS
  - Beware of ***autonomic dysreflexia*** if injury ***above T6***
  - May require general anesthetic secondary to pain, if the patient has partial sensation intact
  - Retrograde ejaculation is common; catheterize bladder for semen specimen

Sperm Retrieval Recommendations

Non-obstructive Azoospermia: TESE or microTESE

Obstructive: surgeon preference / expertise

SPERMATOGENESIS TO FERTILIZATION

- ***Spermatogenesis***: production of mature sperm
  - Begins in the seminiferous tubules and supported by Sertoli cells
  - Spermatogonium (2n) mitosis → primary spermatocyte (2n)
  - Primary spermatocyte (2n) meiosis I → secondary spermatocytes (1n)
  - Secondary spermatocyte (1n) meiosis II → spermatid (1n)
  - Spermatid (1n) differentiation → sperm
  - Complete spermatogenesis takes ~ ***72-74 days***
    - Testicle: ~ 64 days
    - Epididymis: ~ 10 days
  - Temperature dependent; requires ***34-35°C*** (normal body temperature is 37°C)
- ***Epididymis***
  - Sperm ***maturation***: sperm become motile
  - Sperm ***storage***: majority in tail awaiting emission
  - Sperm travel time through the epididymis ***10-14 days***

Epididymal Sperm

Most proximal site of motile sperm

(Important if desire for artificial insemination)

- ***Erection***: penile tumescence
    - Parasympathetic autonomic system (***S2-S4; cavernosal nerves***)
- ***Emission***: ejaculate deposited into the urethra
    - Sympathetic autonomic system (***T10-L2; hypogastric nerves***)
- ***Ejaculation***: discharge of ejaculate out of the urethra
    - Somatic input (***S2-S4; pudendal nerve***)
    - Pre-ejaculate from Cowper's glands to neutralize the urethral fluid
    - Sperm are viable after ejaculation for ***48-72 hours*** within the female reproductive system

See the Sexual Dysfunction Chapter for further details on pathophysiology of erection, emission, and ejaculation.

SEMEN COMPOSITION

Fluid Origin	Contribution	pH*	Notes
Seminal vesicle	60-80%	> 7 (basic)	Fructose
Prostate	10-20%	< 6.5 (acidic)	PSA (liquefaction); Semenogelin (prevents capacitation); Citric acid; Zinc; prostatic acid phosphatase
Sperm	< 10%		From tail of the epididymis (cauda)

** Overall semen pH is basic (7.2-8), and normal vaginal pH is acidic (3.8-4.5)*

- ***Capacitation***: complex reactions that lead to sperm fertility
    - Occurs within the ***vaginal vault*** with an increased pH
    - Influx of calcium leads to hypermobility that aids in traversing the cervix
    - The sperm obtains its greatest mobility in the female genital tract
- ***Acrosomal reaction***: allows for sperm penetration into the ovum
    - Sperm binds the ovum, and then initiates the acrosomal reaction
    - Exocytosis reaction allowing penetration of the zona pellucida, then sperm and oocyte plasma membrane fusion. The sperm nucleus enters the ovum.
- ***Fertilization***: sperm and ovum nuclei fuse within the ovum, and then implant into the endometrium

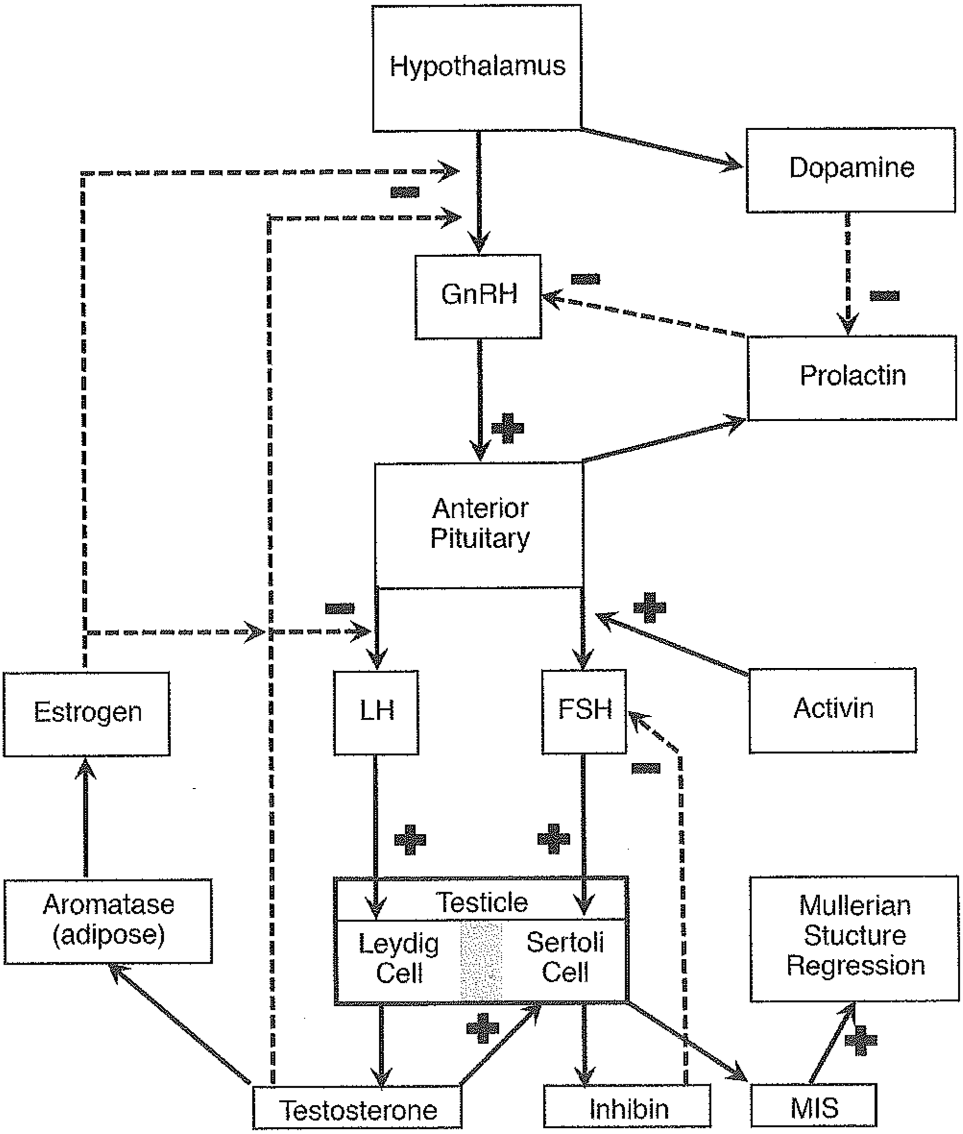
Fertilization

Most common location: ampulla of the fallopian tube

HYPOTHALAMIC-PITUITARY-TESTICULAR HORMONAL AXIS

- **Hypothalamus**
    - Synthesizes and releases ***GnRH*** episodically to simulate anterior pituitary (gonadotropin-releasing hormone; aka luteinizing hormone-releasing hormone, LHRH)
    - Testosterone / estrogen have negative feedback on GnRH release
- **Anterior Pituitary** (stimulated by GnRH)
    - Releases ***FSH*** (follicle stimulating hormone)
        - Stimulates Sertoli cells spermatogenesis
        - FSH is inhibited by ***inhibin*** produced by Sertoli cells
        - FSH is stimulated by ***activin*** produced by multiple organs
    - Releases ***LH*** (luteinizing hormone)
        - Stimulates Leydig cells to release testosterone

    - ***Normal testosterone:estrogen ratio is 10:1*** (males)
    - ***Aromatase***: converts testosterone to estrogen, and vice versa
  - Releases ***prolactin***
    - Elevated prolactin levels ***suppress GnRH*** (thus FSH/LH)
    - Dopamine inhibits prolactin release
- **Testicle**
  - **Leydig cells** (stimulated by LH)
    - Produce ***testosterone*** and other androgens
  - **Sertoli cells** (stimulated by FSH)
    - Responsible for ***spermatogenesis***
    - Produces ***Inhibin*** as a negative feedback on FSH
    - Produces ***androgen-binding protein*** within seminiferous tubules to bind testosterone / dihydrotestosterone. This results in the elevated androgen levels needed for spermatogenesis.
    - Produce ***mullerian inhibitory substance*** (MIS) as a fetus
    - Produce lactate, estradiol, transferrin
    - Line the seminiferous tubules and form the ***blood-testis barrier***


Hypothalamus
Dopamine
GnRH
Prolactin
Anterior Pituitary
Estrogen
LH
FSH
Activin
Aromatase (adipose)
Testicle
Leydig Cell
Sertoli Cell
Mullerian Stucture Regression
Testosterone
Inhibin
MIS

Initial Male Infertility Evaluation

Medical history

Physical exam

Semen Analysis x 2

Serum FSH and Testosterone

| PHYSICAL EXAM |

- Normal ***testicular volume*** is ***≥ 20 mL***
    - Calculated with the empiric formula of Lambert: Length x Width x Height x 0.71
- **Normal adult testicular size**: 5cm x 3cm x 2cm
- Evaluate the penis / urethral meatus: rule out meatal stenosis and hypospadias
- ***Vas deferens*** presence or absence – unilateral or bilateral
    - If Congenital Bilateral Absence of Vas Deferens (CBAVD), check for ***CFTR gene mutation*** on chromosome 7 (i.e. cystic fibrosis)
        - There are many potential CFTR gene mutations identified
        - Genetic counseling is highly encouraged
- Evaluate for ***secondary sex characteristics***
    - If absence, concern for disorders of sex development
- ***Varicocele***: ~ 40% of infertile men
    - Majority are on left side (90%); if right side varicocele check renal ultrasound to rule out mass
    - Semen analysis: Teratospermia, Asthenospermia, Azoospermia

VARICOCELE GRADING

Grade	Description
Subclinical	Only seen on ultrasound, not palpable
1	Palpable with valsalva
2	Palpable without valsalva
3	Visible without palpation

- o Indication for Varicocele Repair:
  - * Palpable varicoceles (i.e. grade 1-3) AND abnormal semen analysis
  - * Adolescents with a palpable varicocele and ipsilateral testicular size discrepancy (> 4 mL)
  - * ~ 2/3 semen analysis improve (monitor every 3 months)
  - * 30-60% pregnancy rate (controversial data)
- o If palpable varicocele, normal semen analysis, and desire for future fertility, then routinely recheck a semen analysis every 1-2 years. If a semen abnormality is noted on recheck, consider varicocele repair.

- Evaluate for ***exposure to gonadotoxins***: smoking, alcohol, marijuana, illicit drugs, chemotherapeutics, radiation, medications altering the hypothalamus-pituitary-testis axis (e.g. leuprolide, antidepressants), heavy metals, insecticides, pesticides, and hot tubes (elevates scrotal temperature)

| SEMEN ANALYSIS |

COLLECTION

- Abstinence 48-72 hours prior collection
- Keep sample at room or body temperature (no refrigeration)
- Analyze sample within 1 hour of collection
- At least 2 semen samples separated in time are required for proper analysis
- If febrile illness in past 3 months, repeat sample in 4-8 weeks (allow for spermatogenesis)
- Sperm concentration is performed after centrifuged

SEMEN ANALYSIS CHARACTERISTICS

Parameter	Reference Range
Volume	≥ 1.5 mL
pH	7.2-8.0
Sperm Concentration	≥ 15 million/mL
Total Sperm Count	≥ 39 million
Total Motility	≥ 40%
Progressive Motility	≥ 32%
Vitality (nigrosin-eosin stain)*	≥ 58% (alive)
Morphology	≥ 4% (Kruger strict criteria)
Leukocyte count	< 1 million/mL
Fructose	Present

** Necrospermia (dead sperm) stain pink/red*

- ***Intratesticular arterial resistive index > 0.6*** via Doppler ultrasound may indicate abnormal sperm count. (Normal RI is ~ 0.5 for intratesticular arteries)

NO ABNORMALITIES

- Requires at least 2 normal semen analysis
- Perform female evaluation
    - o ***Age < 40 is most important female characteristic for pregnancy***
- If female evaluation is normal, then consider anti-sperm antibodies and sperm chromatin assay
    - o **Sperm Chromatin Structure Assay (SCSA)**: determines the DNA fractionation index, which is predictive of assisted reproduction outcomes (lower index has a better outcome)
        - * There is currently no treatment for abnormal DNA integrity

VOLUME ABNORMALITIES

- ***Incomplete collection*** or ***retrograde ejaculation*** = low ejaculate volume (< 1 mL) and normal pH
    - o Review method and recollect to rule out incomplete collection
    - o Post-ejaculation urinary analysis to rule out presence of sperm (i.e. retrograde ejaculation)

Post-Ejaculate Urinalysis

Indicated if ejaculate volume < 1 mL

(Exceptions: hypogonadism and CBAVD)

- ***Ejaculatory duct obstruction or absence of seminal vesicle*** = low ejaculate volume and acidic pH
    - o Transrectal ultrasound: ejaculatory obstruction (results in large distended seminal vesicles) vs. absence of seminal vesicles
- ***Hypogonadism***: low testosterone will lead to decreased ejaculate volumes

- ***Hyperspermia***: increased ejaculate volume (>5.5 mL)
  - o Large semen volume leads to dilute sperm concentration
  - o Tx: mechanical concentration with intrauterine insemination

AZOOSPERMIA

- Requires at least 2 centrifuged semen analysis without sperm present
- Lab: ***FSH, total serum testosterone*** should be check in all azoospermic patients (~99% of abnormalities will be identified with these 2 tests)
  - o If above labs are abnormal, check ***prolactin and LH***, and consider ***TSH***
- If ***non-obstructive*** azoospermia and requiring sperm retrieval for IVF / ICSI, testicular sperm is the best method because it has the highest likelihood of sperm presence at the origin of spermatogenesis. If ***obstructive*** azoospermia, anywhere "up stream" from the obstruction will likely locate sperm.

AZOOSPERMIA: OBSTRUCTIVE VS. NON-OBSTRUCTIVE

Azoospermia	FSH	Longitudinal Axis of Testis	Diagnostic Positive Predictive Value
Obstructive	≤ 7.6	> 4.6 cm	96%
Non-obstructive	> 7.6	≤ 4.6 cm	89%

Schoor RA, et al. J Urol. 2002;167:197–200.

- Pre-testicular: endocrine abnormalities
  - o ***Hypogonadotropic hypogonadism (secondary testicular failure)***
    - * Low FSH, LH, and testosterone; bilateral testicular atrophy and pituitary disorder
    - * **Prolactin**: hyperprolactinemia inhibits GnRH and may indicate a pituitary adenoma

    - **Hypothalamic-pituitary MRI**: rule out pituitary adenoma, empty sella syndrome
  - ***Kallmann Syndrome***
    - Congenital hypogonadotropic hypogonadism and anosmia
    - Low FSH, LH, and testosterone
    - Delayed puberty
  - ***Androgenic anabolic steroids***: induces hypogonadal hypogonadism; normal hormonal function may or may not return once exogenous administration is stopped.
    - Exogenous androgens ***suppress GnRH***
    - Bilateral testicular atrophy; normal or increased seminal vesical fluid
    - If hypogonadism and interested in fertility in future, do not treat with exogenous testosterone. Treat with ***Clomiphene*** (selective estrogen receptor modulator, SERM) or ***Anastrozole*** (aromatase inhibitor) to allow continued spermatogenesis.
    - **Clomiphene**: inhibits estrogen's negative feedback pathway on the hypothalamus and pituitary gland
      - Increases FSH, LH, testosterone, and estradiol (via aromatase)

Azoospermia + Hypogonadotropic Hypogonadism

Check serum prolactin and pituitary imaging

- **Testicular**: spermatogenesis disorder
  - ***Hypergonadotropic hypogonadism (primary testicular failure)***
    - High FSH and LH, low testosterone, bilateral testicular atrophy
    - **Karyotype**: 5-10% will be abnormal; most commonly (2/3) ***Klinefelter Syndrome (47 XXY)***

    - A karyotype is also indicated if severe oligospermia (< 5 million/mL)
  - **Y-chromosome microdeletion (Yq11)**: 10-15%.
    - ***AZFa / AZFb***: unable to perform ICSI (adoption only)
    - ***AZFc***: possible to perform ICSI via TESE (80%)
      - ***DAZ gene*** is located on the AZFc region, and crucial for spermatogenesis
    - Note: microdeletions are found on the long arm (Yq), and the testis-determining factor is found on the short arm (Yp) of the Y chromosome. Will be passed on to male children if ICSI performed
  - Testicular biopsy usually unnecessary unless ICSI is desired

Kallmann vs. Klinefelter Syndrome

Kallmann: ***hypo***gonadotropic hypogonadism (low FSH/LH)

Klinefelter: ***hyper***gonadotropic hypogonadism (high FSH/LH)

- ***Sertoli Cell-Only Syndrome (Germ Cell Aplasia)***
  - Leydig and Sertoli cells are present, but lacking germ cells
  - Elevated FSH, normal LH/testosterone
    - Leydig cell failure is compensated, thus allowing for normal testosterone
  - Etiology: idiopathic, Y-chromosome microdeletion, Klinefelter syndrome, radiation exposure
  - May try testicular biopsy for possible sperm retrieval for ICSI/IVF, but unlikely

Azoospermia + Hypergonadotropic Hypogonadism

Check karyotype and Y-chromosome microdeletion assay

(offer testing to all non-obstructive azoospermia patients)

- **Post-testicular**: ejaculatory dysfunction / obstruction
    - ***Vas Deferens absence***
        - Low semen volume and acidic semen
        - 2/3 of ***CBAVD*** have CFTR gene mutation (***cystic fibrosis***)
            - Determine if female is a cystic fibrosis carrier (~ 5%)
        - If unilateral vasal agenesis, likely contralateral, partial or complete vasal atresia
        - Renal ultrasound: rule out renal agenesis (25% unilateral, 10% bilateral vas deferens absence)
        - Tx: IVF/ICSI
    - ***Ductal obstruction / dysfunction***
        - Low semen volume and normal sized testicles
        - If low ejaculate volume, normal sized testicles and vas deferens, check **seminal pH, fructose, and transrectal ultrasound** (TRUS)
            - Ejaculatory duct obstruction on TRUS: midline cysts, dilated ejaculatory ducts and/or dilated seminal vesicle ***(> 1.5 cm*** in anterior-posterior diameter)
            - Seminal vesical aspiration: if high sperm count = obstruction. Consider **seminal vesiculogram** to identify obstruction
            - Tx: transurethral resection of ejaculatory ducts

Fructose

Indicates patency of seminal vesicles

- * If normal ejaculate volume, normal FSH, at least 1 vas deferens and azoospermia requires diagnostic **testicular biopsy**
  - Do not place biopsy in formalin!
  - If normal biopsy: obstructive azoospermia
  - If no sperm is in the epididymis: intratesticular obstruction and will require IVF or ICSI for pregnancy
  - Do not perform vasogram, unless planning to perform concurrent vasoepididymostomy at same time

o ***Young's Syndrome***

- * Obstructive azoospermia, bronchiectasis, sinusitis
- * Abnormally thick epididymal secretions results in obstructive azoospermia
- * Tx: IVF/ICSI

o ***Previous vasectomy***

- * Iatrogenic obstruction – most common cause of azoospermia
  - In patients that have not undergone vasectomy, the most common ductal obstruction is found in the epididymis
- * Intraoperative vasal fluid analysis from the testicular end of the vas deferens is collected and will guide procedural technique: vasovasostomy vs. vasoepididymostomy.
- * ***Vasovasostomy***: Majority of men will have return of sperm within their semen; however, pregnancy rates vary between 30-75%. Time since vasectomy (i.e. ***obstructive interval***) is most important prognostic indicator
  - < 3 years, the pregnancy rate is ~ 75%

        - ≥ 15 years, the pregnancy rate is only ~ 33%
        - Indication: intraoperative vasal fluid analysis demonstrates **sperm, or clear fluid without sperm**
    - ***Vasoepididymostomy***: ~ 60-80% patency rate, and pregnancy rates of 25-45%, depending on the female partner's age and time since vasectomy
        - Indications: intraoperative vasal fluid analysis demonstrates **thick fluid without sperm** (increased risk with increased obstructive interval)
    - If the female is > 37 years old and/or ≥ 15 years since vasectomy, consider ICSI.
    - If the female is ≥ 40 years old, evaluate for fertility prior to vasectomy reversal or ICSI.
    - May take up to 1 year for return of sperm to ejaculate

MOTILITY ABNORMALITIES

- Most common isolated abnormal sperm parameter (asthenospermia)
- Progressive motility refers to sperm with forward movement
- Total motility refers to sperm with any movement including progressive and non-progressive movements
- ***Kartagener's Syndrome (Primary Ciliary Dyskinesia)***
    - Autosomal recessive
    - Situs inversus, chronic sinusitis, bronchiectasis
    - Immotile sperm despite normal concentration
- ***Anti-sperm antibodies***
    - Results in sperm agglutination, which decreases motility
    - ***Only IgA and IgG*** are found in the male genital tract
    - Indications: isolated asthenospermia with normal sperm concentration; sperm agglutination; abnormal post-coital test
    - Testing (IgA, IgG) is unneeded if planning to proceed with ICSI

- ***Genital tract infections / sexual transmitted diseases***
    - Antibodies to the infection cause sperm agglutination
    - Tx: treat infection and recheck semen analysis in 3 months
- Tx: empiric antioxidants (vitamin C and Zinc), ICSI

SPERM MORPHOLOGY

- Etiology: multifactorial
- **Kruger Strict Analysis**: determines sperm morphology
    - 200 sperm are individually counted and the morphology is analyzed
    - Percent of normal forms is calculated. Previous categories are:
        - ≥ 15% is normal/good
        - 4-14% was suboptimal (now considered normal)
        - < 4% is poor prognosis
    - As a solitary finding, management is controversial
- ***Round headed sperm***
    - Lack acrosome, so will not be able to penetrate the ovum
    - Tx: ICSI

OLIGOASTHENOTERATOZOOSPERMIA

- Etiology multifactorial
- Tx: Coenzyme Q_{10} (Ubiquinol) has shown improvement of sperm concentration, motility, and morphology

SUMMARY OF SERUM INFERTILITY FINDINGS

Disorder	FSH	LH	Testosterone	Prolactin
Primary testicular failure (Hypergonadotropic hypogonadism)	↑	↑	↓	Normal
Sertoli cell-only syndrome	↑	↑	Normal	Normal
Klinefelter's syndrome	↑	↑	↓	↑ / Normal
Secondary testicular failure (Hypogonadotropic hypogonadism)	↓	↓	↓	Normal
Hyperprolactinemia	↓	↓	↓	↑

SUMMARY OF SEMEN ANALYSIS AND POSSIBLE DIAGNOSES

Abnormality	Differential Diagnoses
Volume	Retrograde ejaculation, incomplete collection, absence of seminal vesicles
pH	Absence of seminal vesicles, ejaculate duct obstruction
Sperm Concentration – pre-testicular	Secondary testicular failure, Kallmann syndrome, anabolic steroids, Klinefelter's syndrome
Sperm Concentration - testicular	Primary testicular failure, Y-chromosome microdeletion, Sertoli cell-only syndrome, varicocele
Sperm Concentration – post-testicular	CBAVD, cystic fibrosis, ejaculate duct obstruction, Young syndrome, vasectomy
Motility	Kartagener's Syndrome, anti-sperm antibodies, genital tract obstruction, varicocele, sperm agglutination
Vitality (nigrosin-eosin stain)	Infection, genetic, toxins, varicocele, testes heat exposure, medications
Morphology	Varicocele, round headed sperm, genetic defects
Leukocyte count	Infection, smoking, alcohol
Fructose	Seminal vesicle absence, ejaculatory duct obstruction

CHAPTER 27: INTERSEXUALITY / DSD

It is crucial to review the embryology and physiology of genitourinary development to understand the clinical manifestations and lab abnormalities associated with disorders of sexual development.

| DISORDERS OF GONADAL DIFFERENTIATION |

Seminiferous Tubule Dysgenesis

47, XXY (KLINEFELTER SYNDROME)

- Approximately 1:1000 births
- ***Primary testicular failure*** with ***at least one Y and two X chromosomes***
    - Mosaic pattern is the most common (46, XY / 47, XXY)
- Seminiferous tubule degeneration and hyalinization
- Most common hypogonadism / infertility associated chromosomal disorder
    - Classically infertile; however, up to 50% may father with current assisted reproductive technology
- Sx: ***tall stature with eunuchoid body habitus***, small testes, ***azoospermia***, oligospermia, postpubertal gynecomastia with increased risk for ***breast carcinoma*** and non-Hodgkin's lymphoma, cognitive disability
- Lab: ***elevated FSH*** (loss of Sertoli cells, thus no inhibin present to limit FSH)

  - ***Low testosterone with elevated LH*** (loss of Leydig cells = primary failure)
- Tx: testosterone replacement therapy (TRT) started at puberty, reduction mammoplasty prn, routine breast exam because increased breast cancer risk
  - If symptomatic hypogonadism and history of breast cancer (majority estrogen receptor positive), treat with ***aromatase inhibitors*** (i.e. Anastrozole), which not only increases testosterone, but decreases estrogen levels.

46, XX MALES

- Approximately 1:20,000 males
- Majority are secondary to ***SRY translocation to the X chromosome***; seminiferous tubule hyalinization
- Phenotype: male external genitalia (increased hypospadias incidence), 100% infertile, hypogonadism, gynecomastia, azoospermia
- Tx: consider TRT, monitor gynecomastia

Syndromes of Gonadal Dysgenesis

45, XO TURNER SYNDROME

- 1: 2500 female live births; 15% of spontaneous abortions
- ***Premature ovarian failure*** with ***only one X chromosome***
- Phenotype: female genitalia with lack of secondary sexual development, ***primary amenorrhea***, ***streak ovaries***, infertility
- Associated ***horseshoe kidney***, ***aortic coarctation***, ***webbed neck*** (lymphedema in utero), short stature, hypothyroidism, shield chest, cognitive disability
- Lab: primary hypogonadism (low estrogen/androgen, elevated FSH/LH)
  - All tested for Y chromosome material
    - ***If any Y present: gonadectomy for risk of malignant gonadoblastoma*** (i.e. Turner mosaic 45XO/46XY)
- Tx: consider growth hormone and estrogen/progesterone cycling at puberty

  - Classically infertile; however, pregnancy may be possible with assisted reproductive technology

NOTE: *do NOT confuse with* **NOONAN'S SYNDROME**

  - ***Somatic chromosomal defect*** (not sex chromosome)
    - Associated genes: PTPN11, SOS1, RAF1, KRAS
  - Confused as "Male Turner's Syndrome"; however, there is equal male to female distribution
  - Phenotype: normal genitalia
  - Webbed neck, short stature, shield chest, cognitive disability, hypertelorism, down slanting eyes, congenital heart disease
  - Lab: normal sex hormone levels, FSH, LH

COMPLETE GONADAL DYSGENESIS

46, XY (SWYER SYNDROME)

- Complete dysgenesis results in ***streak gonads***, thus ***lack of testicular testosterone, DHT, or Mullerian inhibiting substance***
- Phenotype: normal female genitalia with bilateral streak gonads (infertile)
  - Most present as young females with delayed puberty / amenorrhea
- Tx: high risk for gonadoblastoma, so all will need ***gonadectomy***; estrogen/progesterone cycling at puberty

46, XX

- Complete dysgenesis results in ***streak gonads***, thus ***lack estrogen / progesterone***
  - Sexual infantilism
- Phenotype: normal female genitalia with bilateral streak gonads (infertile)
- Tx: estrogen/progesterone cycling at puberty; however, does ***not*** need gonadectomy because lack of Y chromosomal material

45, XO / 46, XY MIXED GONADAL DYSGENESIS

- 2nd most common form of DSD

- ***Unilateral testicle*** with ***contralateral streak gonad*** and ***persistent Mullerian structures*** (i.e. Fallopian tube, uterus, superior vagina)
  - The testicle results in varying degrees of ***external genitalia masculinization***
- Phenotype: variable pending chromosomal percentage: Turner's to ambiguous to normal male
  - Majority diagnosed by amniocentesis will have a normal male phenotype
- Tx: ***streak gonadectomy*** (if male assignment) or ***bilateral gonadectomy*** (if female assignment...Y chromosome present); hormone supplementation prn

True Hermaphrodite

46,XX/46,XY OVOTESTICULAR DSD

- Rarest form of DSD
- Either ***one ovary and one testicle*** (1/3); or one or both gonads are ***ovotestis*** (2/3; ovarian and testicular tissue present in same gonad)
- Chromosomes: 46,XX > XX/XY > XY
  - 46, XX may be fertile
  - 46, XY are infertile
- Phenotype: ambiguous external genitalia, but will be masculinized due to testicular tissue
  - If testicle = ipsilateral vas deferens
  - If ovary = ipsilateral fallopian tube
  - If ovotestis = fallopian tube, vas deferens or both present
- Tx: assign gender and remove opposing gonadal tissue

Embryonic Testicular Regression and Bilateral Vanishing Testes Syndrome

- Group of disorders that are seen in 46, XY patients lacking testicles at birth, but have evidence of testicular function at some point as a fetus
  - Etiology includes ***bilateral extravaginal torsion***, genetic mutation, teratogens

BILATERAL VANISHING TESTES SYNDROME

- Loss of testicular tissue after MIS production and Wolffian duct generation; however, underdeveloped external genitalia (e.g. absent prostate, micropenis)
- Tx: hormone supplementation

EMBRYONIC TESTICULAR REGRESSION

- Loss of testicular tissue after MIS is produced resulting in ambiguous genitalia without Mullerian structures

| 46,XY DSD (FEMININE MALE) |

Formerly male pseudohermaphrodite

LEYDIG CELL APLASIA / LH RECEPTOR ABNORMALITY

- 46, XY; autosomal recessive
- Lack of Leydig cells or LH receptor effectively results in ***lack of testosterone and associated embryologic, testosterone-dependent genitalia***
- Phenotype: normal external, female genitalia; however, ***lacks Mullerian structures*** (Sertoli cells produce MIS inhibiting fallopian tubes, uterus, and superior vagina)
- Undescended testicles (UDT) or located in labia majora (female scrotal equivalent), sexual infantilism, lack of post-pubertal changes, infertile

Disorders of Testosterone Biosynthesis

- All disorders are autosomal recessive
- These disorders result from an abnormality of enzymatic conversion of cholesterol to testosterone resulting in incomplete or absent virilization
- ***No Mullerian structures in this group (normal Sertoli cells)***

STAR (20-22 DESMOLASE) DEFICIENCY

- Inability to convert ***cholesterol to pregnenolone*** inhibits entry into the steroidogenesis pathway

  - Lack of mineralocorticoids, glucocorticoids, and sex hormones
- Phenotype: varies from normal female to ambiguous external genitalia
- Sx: UDT, severe adrenal insufficiency (large lipid-laden adrenals)
- Tx: female assignment (no testosterone brain imprinting); gonadectomy; mineralocorticoid, glucocorticoid, and hormonal supplementation

17 ALPHA-HYDROXYLASE DEFICIENCY

- Inability to convert ***pregnenolone to 17-hydroxypregnenolone***
  - Lack glucocorticoids, androgens
- Phenotype: variable: female with blind ending vagina to male with proximal hypospadias and chordee
- Sx: HTN (increased mineralocorticoids)
- Tx: glucocorticoid supplementation to decrease overall steroidogenesis activation

17,20 LYASE DEFICIENCY

- Inability to convert ***17-hydroxypregnenolone to DHEA***
  - Lacks androgen; normal glucocorticoids / mineralocorticoids
- Phenotype: ambiguous genitalia
- Tx: hormone supplementation prn

17 BETA-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY

- Inability to convert ***androstenedione to testosterone*** and ***estrone to estradiol***
- Phenotype: normal external female genitalia at birth with phallic growth and secondary sex characteristics at puberty
  - ***Similar effect as 5-alpha reductase deficiency***
- Sx: UDT, normal Wolffian ducts
- Lab: high androstenedione:testosterone ratio, low testosterone, high LH/FSH
- Tx: gender assignment, hormone supplementation
  - Male = orchidopexy, genital reconstruction
  - Female = orchiectomy, genital reconstruction

Androgen Receptor Defects

ANDROGEN INSENSITIVITY SYNDROME (TESTICULAR FEMINIZATION)

- 46, XY male with testes and variable feminization / ambiguous genitalia
- Androgen receptor is ***Xq11-12***
- Either decreased receptors or receptor affinity
- Up to 1/3 may have rudimentary uterus
- ***Complete Insensitivity***
  - Female external genitalia and secondary sex characteristics
  - Dx: Primary amenorrhea or an inguinal hernia containing a testicle
  - Tx: gonadectomy at puberty
- ***Partial Insensitivity (Reifenstein Syndrome)***
  - Proximal hypospadias, UDT, rudimentary Wolffian ducts, gynecomastia
  - Tx: testosterone supplementation for virilization

DHT Deficiency

5-ALPHA REDUCTASE II DEFICIENCY

- 46, XY autosomal recessive
- Inhibits conversion of ***testosterone to dihydrotestosterone***
- Phenotype: variable: proximal hypospadias to ambiguous genitalia
  - "Pseudovaginal perineoscrotal hypospadias"
- Tx: gender assignment with appropriate hormone supplementation

Guevedoces

"Penis at 12 years" in Dominican Republic culture;

Raised as female, then penis development at puberty

Persistent Mullerian Duct Syndrome

MIS DEFICIENCY (HERNIA UTERI INGUINALIS)

- 46, XY; X-linked autosomal recessive or sporadic
- Male without production of MIS or lack of MIS receptors results in persistent Mullerian ducts (Fallopian tubes, uterus)
- Phenotype: normal external male genitals; usually UDT; Mullerian structures usually located in the inguinal hernia
- Tx: orchidopexy, removal of Mullerian ducts

| 46,XX DSD (MASCULINIZED FEMALE) |

Formerly female pseudohermaphrodite

Congenital Adrenal Hyperplasia (CAH)

21-HYDROXYLASE DEFICIENCY

- Most common form of DSD and 90+% of all CAH
- 46, XY autosomal recessive, ***CYP21A2*** gene loss/mutation on chromosome ***6p21***
- Inability to convert progesterone to 11-deoxycorticosterone and 17-hydroxyprogesterone to 11-deoxycortisol
- May occur in females (majority) or males
    - o Males: ***"Little Hercules"*** - precocious puberty at 2-3 years old with normal genitals; may have salt-wasting from lack of mineralocorticoid
        - * ***Testicular Adrenal Rest Tumors (TART)***: ectopic, hyperplastic adrenal tissue found in the testicle; increases in size with ACTH; usually bilateral and multiple
            - Histologically: appears as Leydig cells without Reinke crystals
            - Tx: ***glucocorticoids decreases ACTH, thus tumor regression***
    - o Females: variable ambiguous genitalia (clitoromegaly to penis); lack secondary female sex characteristics; Mullerian structures present (lack MIS)
- Lab: ***elevated 17-hydroxyprogesterone, androstenedione, ACTH***
- Salt wasting type (75%) – classic form
    - o Lack mineralocorticoid (i.e. aldosterone)
    - o Adrenal crises in first weeks of life and may die
    - o Reason all newborns are screened in USA
- Simple virilization (25%)
    - o Mineralocorticoid activity is present
- Latent Deficiency

  - *o* Presents at puberty; commonly mistaken for polycystic ovarian syndrome
- Tx: glucocorticoid / mineralocorticoid supplementation

11-BETA-HYDROXYLASE DEFICIENCY

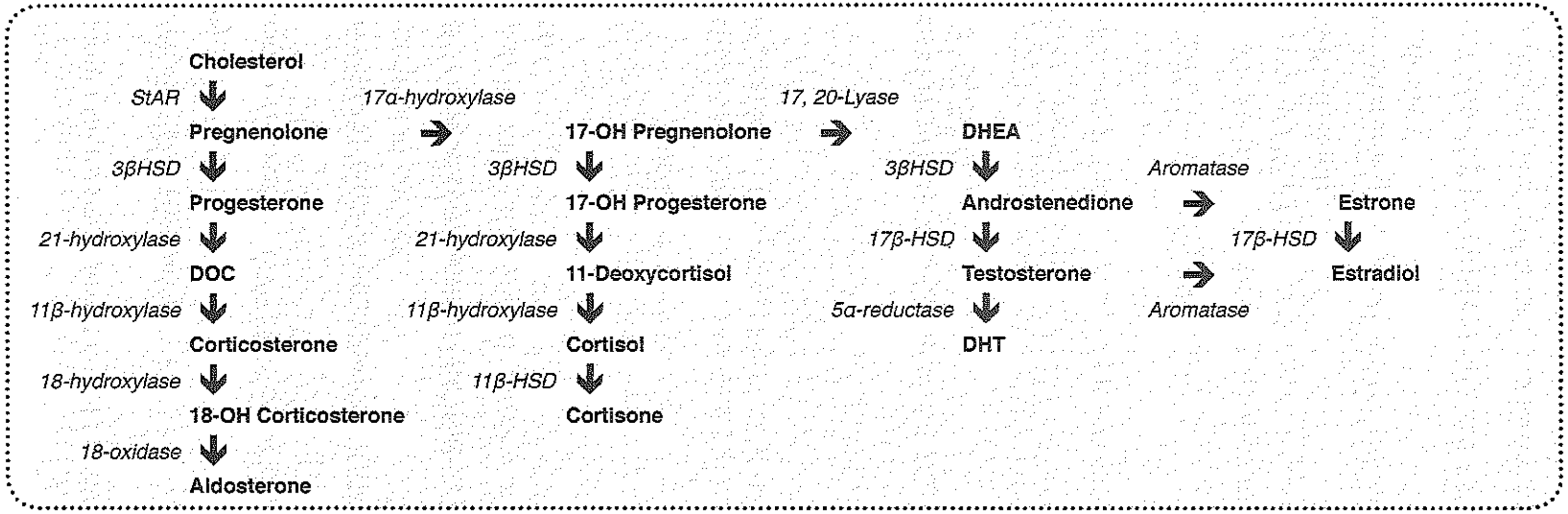
- Approximately 5% of CAH
- 46, XX autosomal recessive, ***CYP11B1*** gene loss/mutation on ***chromosome 8***
- Inability to convert 11-deoxycorticosterone (DOC) to corticosterone and 11-deoxycortisol to cortisol
- Lab: ***elevated 17-hydroxyprogesterone and DOC***
  - *o* HTN due to mineralocorticoid effects of DOC causing salt retention

Urinary Pregnanetriol

Metabolite of 17-hydroxyprogesterone; therefore, its elevation suggests 21-hydroxylase or 11-β hydroxylase deficiencies

3-BETA-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY

- Approximately 1% of CAH
- Inability to convert dehydroepiandrosterone (DHEA) to androstenedione, 17-alpha hydroxypregnenolone to 17-alpha hydroxyprogesterone (glucocorticoids), and pregnenolone to progesterone (mineralocorticoids)
- Phenotype: occurs in males and females
  - *o* Male: variable (e.g. micropenis / hypospadias to blind-ending vagina); normal Wolffian ducts (high DHEA) and lacks Mullerian ducts (MIS present)
  - *o* Female: clitoromegaly, labial fusion (remember DHEA is only weak androgen)
- Lab: ***elevated 17-hydroxypregnenolone and DHEA***
- Tx: mineralocorticoid, glucocorticoid, and hormonal supplementation



StAR = steroidogenic acute regulatory protein, DHEA = dehydroepiandrosterone, DHT = dihydrotestosterone, DOC = 11-deoxycorticosterone, 3βHSD = 3 beta-hydroxysteroid dehydrogenase, 11β-HSD = 11 beta- hydroxysteroid dehydrogenase, 17β-HSD = 17 beta-hydroxysteroid dehydrogenase

SUMMARY OF DISORDERS OF ANDROGEN SYNTHESIS / CAH

Disease	Ambiguous Genitalia	Glucocorticoid	Mineralocorticoids*	Androgens	Incidence
3-β hydroxysteroid dehydrogenase deficiency	males; mild in females	↓	↓	↓	1%
21-hydroxylase deficiency	females	↓	↓	↑	90%
11-β hydroxylase deficiency	females	↓	↑	↑	9%
17-α hydroxylase deficiency	males	normal	↑	↓	rare

** Elevated mineralocorticoids results in hypertension.*

Maternal Exposure to Androgens / Progesterone

- Exogenous hormonal virilization is rare
- Etiologies: ***Danazol*** (testosterone derivative used to treat endometriosis), progesterone, aromatase deficiency, ovarian / adrenal functional tumors

| MISCELLANEOUS |

MAYER-ROKITANSKY-KUSTER-HAUSER (MRKH) SYNDROME

- 46, XX female with defect in ***WNT4 gene*** on chromosome 1p36 that results in ***absent Mullerian (paramesonephric) ducts*** (i.e. uterus, fallopian tubes, superior vagina)
- Phenotype: normal external genitalia with absent uterus and fallopian tubes with variable vagina findings

- Sx: primary amenorrhea, infertile, upper urinary
- Tx: vaginal dilation or neovagina

DENYS-DRASH SYNDROME

- Wilms' tumor, DSD (gonadal dysgenesis), Nephropathy (diffuse mesangial sclerosis)
- ***WT1 gene*** mutation on ***11p13***

Denys-Drash Mnemonic

DenyS-Drash has DSD

FRASIER SYNDROME

- Similar to Denys-Drash, except it has ***gonadoblastoma*** rather than Wilms' tumor
- Streak gonads, focal segmental glomerulosclerosis, gonadoblastoma

WAGR SYNDROME

- **W**ilms' tumor, **A**niridia, **G**enitourinary abnormalities (hypospadias/UDT), **R**etardation (mental)
- ***WT1 gene*** mutation on ***11p13***

GENDER ASSIGNMENT / REASSIGNMENT

- Potential psychiatric consequences
- Difficult to assign gender after brain has been exposed to sex hormones (e.g. assigning a female gender to a child that was exposed to testosterone in utero already has masculinized brain imprinting)
- Assignment is not required immediately at birth

CHAPTER 28: SEXUALLY TRANSMITTED DISEASES

| URETHRITIS |

CHLAMYDIA

- ***Chlamydia trachomatis D-K***
- Incubation 3-14 days; transmission: sex or newborn cervical exposure
- Majority of patients are asymptomatic
- May have clear / white urethral discharge
- Up to 40% of untreated women will progress to pelvic inflammatory disease (PID)
    - Most common cause of PID
- Lab: urethral or endocervical swab; urine nucleic acid amplification tests (NAAT)
- Tx: ***Azithromycin*** (1gm x 1) or ***Doxycycline*** (100mg BID x 7 days)
    - Alt: Erythromycin base, Levofloxacin, Ofloxacin
    - Empirically treat for Gonorrhea

Epididymitis Etiology (Most Common)

Men < 35: Chlamydia and Gonorrhea

Men > 35: E. coli

OTHER NON-GONOCOCCAL URETHRITIS

- ***Ureaplasma urealyticum***
- ***Mycoplasma hominis***
- Lab: specialized urethral swab culture and PCR
    - o Gram stain of urethral swab: ***4 polymorphonuclear leukocytes (PMN) per high powered field = urethritis***
- Tx: ***Doxycycline*** (100mg BID x 7 days) or Azithromycin or tetracycline

GONORRHEA

- ***Neisseria gonorrhoeae***
- Incubation 2-10 days
- Mucopurulent urethral discharge; majority of men are symptomatic, while many women may be asymptomatic
- Common cause of PID
- Lab: urethral or urine NAAT; oxidase positive culture on ***Thayer-Martin*** medium
    - o Urethral swab: ***intracellular gram negative diplococci***
- Tx: ***Ceftriaxone*** (250mg IM x 1) - oral cephalosporins are no longer recommended
    - o Empirically treat for Chlamydia as well
    - o Quinolones are no longer recommended due to high resistance rates in USA
- **Disseminated Gonococcal Infection**: petechial lesions, arthralgia, septic arthritis, perihepatitis
    - o Tx: hospitalization with Ceftriaxone 1gm IV daily

Expedited Partner Therapy (EPT) – Chlamydia & Gonorrhea

Recommendation is for Ceftriaxone 250mg IM and Azithromycin or Doxycycline, which the IM dose limits the effectiveness of EPT; however, EPT is still appropriate in heterosexual partners that are unlikely to seek treatment

PELVIC INFLAMMATORY DISEASE (PID)

- Etiology: ***Chlamydia trachomatis***, Neisseria gonorrhoeae, Ureaplasma urealyticum, Mycoplasma hominis, anaerobes
- Infection / inflammation of the uterus, fallopian tubes and surrounding pelvic structures
- ***Fitz-Hugh-Curtis syndrome***: perihepatitis associated with PID
- May lead to infertility, particularly with recurrent episodes there is an increased risk
- Laparoscopy may be needed for diagnosis
- Tx: treat for Chlamydia and Gonorrhea, and possibly vaginitis

REITER SYNDROME

- ***Autoimmune response to non-gonococcal urethritis, conjunctivitis and arthritis***
- Associated with ***HLA-B27***
- ***Balanitis circinate***: penile glans erythematous plaque or circinate lesion
- Tx: ***Doxycycline,*** NSAIDS, steroids

Reiter Syndrome Mnemonic

Can't pee, can't see, can't climb a tree

| ULCERATIVE LESIONS |

GENITAL HERPES

- ***Herpes Simplex Virus (HSV)***
  - HSV-1: 10-15% (crossover from oral lesions)
  - HSV-2: 85-90%
- Incubation: 1-7 days
- ***Painful ulceration***, bilateral painful inguinal adenopathy
- ***Multiple vesicles / shallow ulcerations with erythematous base***; ***non-neural distribution*** (pathognomonic)
  - Vesicles may coalesce to one larger lesion; this makes the clinical diagnosis more difficult
- Silent infection is common; many patients with HSV-2 antibodies have no history of clinical infection, or only had a single ulceration without recurrence.
  - Clinically, may have constitutional flu-like symptoms during the initial infection
  - First episodes are usually more severe than recurrences
- Asymptomatic viral shedding results in majority of transmissions
- Lab: ***viral culture with subtype***
  - Older test is Tzanck smear, which is positive for herpes simplex and varicella zoster virus
- Tx: Acyclovir, Valacyclovir or Famciclovir
  - May treat episodically (only during outbreaks) or daily suppressive therapy
  - There is currently no cure
- ***Elsberg Syndrome***: acute urinary retention secondary to sacral HSV-2 radiculomyelitis
  - Tx: self-limiting (< 12 weeks), timed voiding, CIC prn

CHANCROID

- ***Haemophilus ducreyi*** (gram negative streptobacillus)
- Incubation: up to 3 weeks
- ***Painful, deep ulceration, gray/yellow exudate*** with shaggy border
- "Kissing lesions" - may spread from apposing skin, such as labia and inner thighs
- Most common in Caribbean and Africa countries
- Lab: rule out other genital lesions (i.e. painful genital ulcer + regional adenopathy + negative HSV and Syphilis tests) because there is not a good serologic marker of this disease
    - Difficult to culture
- Tx: **Azithromycin** (1gm po x 1) or **Ceftriaxone** (250mg IM x 1)
    - Alternatives: Ciprofloxacin, Erythromycin base

SYPHILIS

- ***Treponema pallidum*** (gram negative, spirochete)
- Incubation: 1 week - 3 months; transmission is sexual or congenital
- ***Single, painless, indurated ulcer lasting 3-6 weeks*** with bilateral, non-tender regional adenopathy
- Lab Screening:
    - ***RPR:*** Rapid Plasma Reagin
    - ***VDRL***: Venereal Disease Research Laboratory
        - * Both will convert to negative after 1 year (marker of recent transmission)
- Lab Confirmation:
    - ***FTA-ABS***: Fluorescent Treponemal Antibody-ABSorption
    - ***TP-PA***: Treponema Pallidum Particle Agglutination
    - ***DFA***: Direct Fluorescent Antibody
    - Dark-field microscopy is an older lab test and no longer routinely utilized
        - * The tests above remain positive for life.

SUMMARY OF SYPHILIS

Syphilis	Description	Treatment
Primary Syphilis	Single, painless, genital ulcer 3-6 weeks	Benzathine penicillin G 2.4 million units IM once
Early latent syphilis	***< 1 year*** since acquiring syphilis Seroreactive, but no clinical disease	Benzathine penicillin G 2.4 million units IM once
Late latent syphilis	***> 1 year*** since acquiring syphilis ***or unknown time frame*** Seroreactive, but no clinical disease	Benzathine penicillin G 2.4 million units IM weekly x 3
Secondary syphilis	***Maculopapular rash*** on ***palms and soles***, ***condyloma lata*** (very infectious), hepatitis, immune-complex glomerulonephritis	Benzathine penicillin G 2.4 million units IM once
Tertiary syphilis	Gummas, cardiovascular syphilis (aortitis)	Benzathine penicillin G 2.4 million units IM weekly x 3
Neurosyphilis	Meningitis, ***tabes dorsalis*** (dorsal column demyelination), cranial nerve palsies, optic neuritis, cognitive dysfunction	Aqueous crystalline penicillin G or procaine penicillin

- ***Jarisch-Herxheimer Reaction***: headache, myalgia, fever, tachycardia, tachypnea within the first 24 hours of treatment; likely secondary to endotoxin release during death of bacteria.

LYMPHOGRANULOMA VENEREUM

- ***Chlamydia trachomatis L1, L2, L3***
- Incubation: 3-30 days; rare in the USA
- ***Single, painless ulcer with painful unilateral suppurative inguinal adenopathy*** (usually occurs 2-6 weeks after ulcer resolution)
- Lab: Chlamydia complement fixation titers > 1:64; NAAT; positive Chlamydia cultures are difficult to obtain (30-50%)
- Tx: ***Doxycycline*** (100mg BID x 21 days)
  - o Alt: Erythromycin base 500mg QID x 21 days

GRANULOMA INGUINALE (DONOVANOSIS)

- ***Klebsiella granulomatis*** (intracellular gram negative)
- Incubation: 1-4 weeks, but may be up to 1 year
- ***Nodules erode becoming painless, fleshy, beefy-red ulcers without regional adenopathy***; kissing lesions are common
- Lab: Wright-Giemsa stain shows ***Donovan bodies*** (rod shaped organisms in macrophages)
- Tx: ***Doxycycline*** (100mg BID for 3 weeks or until all lesions resolved)
  - o Alt: Azithromycin, Ciprofloxacin, Erythromycin base, Trimethoprim-sulfamethoxazole

ULCERATIVE STD SUMMARY

STD	Etiology	Ulcer	Adenopathy	Treatment
Herpes	Herpes simplex virus	Multiple ***painful*** ulcers / vesicles	Tender bilateral during outbreak	Acyclovir or Valacyclovir
Chancroid	Haemophilus ducreyi	***Painful***, deep ulceration, gray/ yellow exudate	Painful unilateral	Azithromycin or Ceftriaxone

STD	**Etiology**	**Ulcer**	**Adenopathy**	**Treatment**
Syphilis	Treponema pallidum	Single, ***painless***, indurated ulcer (3-6 weeks)	Bilateral, non-tender	Benzathine penicillin G
Lymphogranuloma Venereum	Chlamydia trachomatis L1, L2, L3	Single, ***painless*** ulcer	Painful, unilateral, ***suppurative***	Doxycycline
Granuloma Inguinale	Klebsiella granulomatis	***Painless***, fleshy, beefy-red ulcers	None	Doxycycline

DDx for genital ulcerations: Behcet's syndrome (aphthous and genital ulcers with uveitis), carcinoma, drug reaction, trauma, lichen planus

| MISCELLANEOUS |

CONDYLOMATA ACUMINATUM (GENITAL WARTS)

- ***Human papillomavirus (HPV)***
  - HPV 6, 11 = 90% of condyloma
  - HPV 16, 18, 31, 33, 35, 39 (and many others) = causes of neoplasia
    - Etiology of cervical cancer, majority of penile and anal cancer
      - Smoking increases dysplastic progression
- Incubation: up to 3 months
- Majority of infections are subclinical or asymptomatic; may have painless genital wart
- ***Buschke-Lowenstein tumor:*** giant, verrucous condyloma acuminatum
- Lab: 3-5% acetic acid on lesions will result in white areas (acetowhite)

    - ***Koilocytes*** on microscopy or Pap smear; PCR
- Tx: many resolve spontaneous, if not, there are many treatments available
    - ***Podofilox*** (0.5% solution or gel every 12 hrs x 3 days, then off 4 days, repeat cycle up to 4 times)
    - **Imiquimod** (5% cream 3 times per week at night for up to 16 weeks)
    - Cryotherapy, Electrosurgery, Carbon dioxide laser, Podophyllin resin 25%, Trichloroacetic acid topical, Surgical excision
- Papillomavirus vaccine (Gardasil®) = quadrivalent HPV recombinant vaccine
    - Indicated in males and females age 9-26 years old
    - Vaccine for HPV 6, 11, 16, 18 subtypes
    - Eliminates 70% of all cervical cancer and 90% of genital warts

TRICHOMONIASIS

- ***Trichomonas vaginalis*** (motile parasite)
- Incubation: 5-28 days
- Increased vaginal pH (> 4.5)
- Majority of patients are asymptomatic; however some will have genital irritation with erythema and dyspareunia
- ***Frothy white, green or yellow discharge***
- Lab: ***trichomonads (flagellated pyriform protozoa)*** on wet mount; vaginal culture
    - Whiff test = positive (10% KOH - potassium hydroxide mixed with vaginal fluid releases volatile amines which has a strong fishy odor)
    - Rapid antigen, DNA and RNA tests are available
- Tx: ***Metronidazole*** (2gm oral x 1 or 500 BID x 7 days)
    - Vaginal suppositories are not recommended

MOLLUSCUM CONTAGIOSUM

- ***DNA poxvirus***
- Round papules with ***central umbilication***
- Lab: on H&E stain, classic cup shaped invagination of the epidermis into the dermis; ***Henderson-Patterson bodies***
- Tx: self limited over several months, cryotherapy, pulsed dye laser, or curettage

PUBIC LICE ("CRABS")

- ***Phthirus pubis*** (louse)
- Lab: microscopic crab
- Tx: ***1% Permethrin***

SCABIES

- ***Sarcoptes scabiei*** (mite)
- Highly contagious parasitic infection
- Tx: ***Permethrin 5% cream*** and all cloths and bedding needs to be washed

NON-SEXUALLY TRANSMITTED VAGINITIS

BACTERIAL VAGINOSIS

- ***Gardnerella vaginalis*** predominates the vaginal flora resulting in vaginitis
- Not a true STD, however associated with having a new sexual partner and multiple partners
- Increased vaginal pH **(> 4.5)**, likely from ***decreased lactobacilli*** (produces hydrogen peroxide)
- May dyspareunia; many patients are asymptomatic except odor; erythema and itching are usually absent
- ***Thin, gray, malodorous discharge***
- Lab: ***clue cells*** on wet mount (vaginal epithelial cells with adherent bacteria)

  - Whiff test = positive
- Tx: ***Metronidazole*** (oral or vaginal suppository) or ***Clindamycin***

VULVOVAGINITIS CANDIDIASIS (YEAST INFECTION)

- ***Candida albicans***
- White, cheesy, vaginal discharge with vulvar irritation and itching
- Vaginal pH < **4.5**
- Lab: yeast or ***pseudohyphae*** on wet mount (better seen on 10% KOH)
- Tx: ***Fluconazole*** (150mg orally x 1) or vaginal suppositories (Miconazole, Clotrimazole, Terconazole)
  - Non-albicans species (C. glabrata, C. krusei) are resistant to -azole medications
  - If Candida UTI, only treat if symptomatic, neutropenia, genitourinary surgery or prosthesis, pregnancy, candida cultured from two different body systems (e.g. urine and blood)
    - May need amphotericin B for sepsis or fluconazole resistance

| HIV / AIDS UROLOGIC IMPLICATIONS |

- Sexual transmitted diseases increase the susceptibility and risk for HIV (particularly ***herpes***)
- Increased risk of genital squamous cell carcinoma (HPV-related) and testicular cancer; erectile dysfunction; epididymitis (fungal, mycobacteria)
- ***HAART*** (Highly Active Anti-Retroviral Therapy) is the treatment regimen for HIV
- ***HIV-associated Nephropathy (HIVAN)***: proteinuria, nephritic syndrome, renal insufficiency
  - ***Focal segmental glomerulosclerosis (FSGS)***
  - May have rapid progression to ESRD (HAART may decrease progression)

Circumcision

Reduces HIV incidence ~ 50%

- ***Kaposi's Sarcoma***: herpes simplex virus type 8 (**HSV-8**) in immunocompromised patients results in cutaneous sarcoma
    - Tx: localized treatment (CO2 laser, cryotherapy, radiation, etc.), and treatment for immunocompromised condition
- ***Protease Inhibitors***: may result in radiolucent renal calculi that are not visible on CT scan imaging

HIV CD4 COUNT-ASSOCIATED INFECTIONS

CD4 Count (cells/μL)	**Common Infections**	**Prophylaxis**
< 200	(1) Pneumocystis jiroveci pneumonia (PCP); (2) Candida	(1) Trimethoprim-sulfamethoxazole; (2) Fluconazole (treatment)
< 100	(1) Cryptococcus (2) Toxoplasmosis	(1) Amphotericin B + Flucytosine; (2) Trimethoprim-sulfamethoxazole
< 50	Mycobacterium avium complex (MAC)	Azithromycin or Clarithromycin

CHAPTER 29: INFECTIONS

| RENAL |

PYELONEPHRITIS

- Bacterial infection of the renal parenchyma
- Sx: acute onset flank pain, fever, costovertebral angle tenderness, dysuria
    - May have recent cystitis – common for ascending infection
- Lab: positive urinalysis, ***leukocyte casts***
    - Most common: ***E. coli***
    - Renal insufficiency is variable, and increased when associated with obstruction
- Imaging: if uncomplicated UTI, imaging is not routinely required; however, if complicated or unresolved pyelonephritis, consider renal ultrasound or CT scan (test of choice)
    - CT: enlarged kidney, wedge-shaped area lacking contrast enhancement (usually in line with renal pyramids because of bacterial reflux into the renal medulla), delayed nephrograms
    - Renal infection continuum: pyelonephritis lobar nephronia (acute focal bacterial nephritis) → renal abscess → perirenal abscess (within Gerota's fascia)→ pararenal abscess (outside Gerota's fascia)
        - * ***Lobar nephronia***: may mimic a renal mass on CT scan; no liquefaction at this state

- Tx: antibiotic therapy is mainstay
    - If associated obstruction: ureteral stent or percutaneous nephrostomy
    - Uncomplicated, outpatient: levofloxacin or ciprofloxacin, trimethoprim-sulfamethoxazole (***7 day treatment; levofloxacin is drug of choice***)
        - If gram positive bacteria: amoxicillin ± clavulanic acid
        - Consider single dose IV ceftriaxone, gentamicin, or levofloxacin prior course of oral antibiotics

Gentamicin Fixed Daily Dose

5-7 mg/kg

If elevated trough, decrease dosing frequency from 24 hours to 36-48 hours

-
    - Uncomplicated, inpatient or Complicated: IV levofloxacin; gentamicin ± amoxicillin; or ceftriaxone ± gentamicin (***IV until clinical improvement, then switch to oral antibiotic for 10-14 days***)
        - If gram positive bacteria: ampicillin-sulbactam
    - Pregnant: IV ceftriaxone, or ampicillin + gentamicin
        - Transition to oral cephalexin
- Follow up: recheck urine cultures ~ 2 weeks after completion of antibiotics to assure bacterial eradication
    - ***If persistent fever > 3-5 days, re-image with a renal CT with contrast to evaluate for abscess formation***

Uropathogenic E. coli (UPEC)

E. coli P fimbria bind to the P blood group antigen on erythrocytes, but also to urothelial cells via a galactose disaccharide, making it a common uropathogen

RENAL ABSCESS

- Currently, gram negative bacteria account for majority of renal abscesses
- Associated with renal calculi, pyelonephritis, VUR, complicated UTI
    - Hematologic renal seeding from recent dental work, IV drug abuse, skin infections/abscess usually results in gram positive infections (Staphylococcus), and have a negative urine analysis
- Sx: cyclic fever/chills, flank pain
- Imaging: CT scan with IV contrast (test of choice)
- Tx: all patients will initially require IV antibiotics
    - ***If < 3cm***: IV antibiotics alone is usually sufficient
    - ***If 3-5cm; or < 3cm and failed conservative treatment***: percutaneous drainage
    - ***If > 5cm***: open surgical drainage, and occasionally nephrectomy

XANTHOGRANULOMATOUS PYELONEPHRITIS (XGP)

- Infectious process that results in a chronically inflamed kidney with destruction of renal parenchyma and loss of renal function
- Associated with UTI (***E. coli and Proteus***), ***nephrolithiasis*** (struvite), diabetes, immunocompromised patients, and ***fistulas***
- More common in females
- Histology: ***lipid laden, foamy macrophages (xanthoma cells)***
    - Histology is required for a definitive diagnosis (may be difficult to differentiate from renal tumor)

- Imaging: CT findings - enlarged kidney with ***bear's paw sign*** and staghorn calculus; poor renal function (minimal or no contrast uptake)
- Tx: nephrectomy with removal of all surrounding infected tissues / fistula
  - Usually open approach, as laparoscopic dissection is quite difficult secondary to loss of tissue planes and inflammation

EMPHYSEMATOUS PYELONEPHRITIS

- Severe gas-producing bacterial infection of the renal parenchyma
- Associated with ***diabetes mellitus***
- Sx: fever, vomiting, flank pain (similar to infected renal colic)
- DDx: ***Post-infarction syndrome*** – occurs after renal embolization
  - Occurs in majority of patients (~75%)
  - Flank pain, fever, nausea/vomiting
  - May also present with renal parenchymal gas, thus mistaken for emphysematous pyelonephritis
  - Treatment is conservative management (pain management, antiemetics)
- Imaging: X-ray – gas over renal shadows; CT scan – ***gas within the renal parenchyma***
  - ***Type 1***: No renal or perirenal fluid collections
    - Higher mortality rate
  - ***Type 2***: Presence of renal or perirenal fluid collections associated with parenchymal gas
- Tx: sepsis protocol treatment in all patients (e.g. aggressive fluid resuscitation, broad spectrum antibiotics, vasopressors)
  - Traditionally, nephrectomy has been the treatment of choice, and should still be consider in patients that do not respond to more conservative treatment
  - Percutaneous nephrostomy tube drainage with broad spectrum antibiotics
- Prognosis: mortality is variable from 10-60%

INFECTED RENAL CYST

- Sx: flank pain, pyrexia, chills
- Dx: ***urine culture is usually negative***
- More commonly seen in polycystic kidney disease and acquired cystic disease (ESRD) secondary to increased quantity of cysts
- Imaging: may be difficult to differentiate between cyst infection, hemorrhage, and pyelonephritis
- Tx: Lipophilic antibiotics penetrate the cysts better: ***ciprofloxacin, trimethoprim/sulfamethoxazole, clindamycin, chloramphenicol***
    - If unable to clear infection, consider percutaneous drainage

RENAL ECHINOCOCCOSIS

- Renal parasitic infection by the canine intestinal tapeworm larva (***Echinococcus granulosus***)
- The larva form a renal cortical, ***hydatid cyst***, which forms ***daughter cysts***
- Host: dog / sheep
- Sx: usually asymptomatic
- Dx: daughter cysts in the urine after cyst rupture; may have eosinophilia
    - Do not aspirate because cyst content spillage may result in anaphylaxis
- Tx: surgical cyst excision; albendazole, praziquantel

| URETER / COLLECTING SYSTEM |

EMPHYSEMATOUS PYELITIS

- Gas-producing bacterial infection of the renal collecting system
- Usually found in non-diabetics
- Imaging: CT scan – ***gas within the collecting system***, not within the renal parenchyma
- Treatment: broad spectrum antibiotics in all patients

  - Consider ureteral stent, particularly if associated with a calculus
- Prognosis: nearly all patients will recover

INFECTED HYDRONEPHROSIS

- ***Infected hydronephrosis***: hydronephrosis with UTI
- ***Pyonephrosis***: more severe infected hydronephrosis that causes renal parenchymal destruction and purulent debris
- Sx: high fever/chills, flank pain, nausea/vomiting, ill-appearing
- Imaging: renal ultrasound – pyonephrosis has echogenic collecting system debris; CT – difficult to determine if pyonephrosis based on Hounsfield units.
- Tx: antibiotics, and either ureteral stent or percutaneous nephrostomy

UTI and Ureteral Obstruction

If an infected hydronephrosis is completely obstructed, the urinalysis and culture may be negative

| BLADDER |

CYSTITIS

- Most common bacteria is ***E. coli*** in men and women
  - In young sexually active women, ***Staphylococcus saprophyticus*** may be cause in up to 20% of UTIs
- ***Uncomplicated vs. complicated cystitis***
  - Uncomplicated: no complicating factors
  - Complicated: urinary tract abnormality, immunosuppression (e.g. diabetes mellitus, HIV, cirrhosis, transplant), pregnancy, hospital acquired infections, recent urinary tract surgery, outlet obstruction
- ***Unresolved UTI***: initial treatment of the UTI did not eradicate the infection; usually secondary to resistant bacteria
- ***Recurrent UTI***: ≥ 2 UTIs in 6 months; or ≥ 3 UTIs in 1 year

- ***Reinfection UTI***: repeated infections at longer intervals or different bacterial species
- ***Persistent UTI***: inability to clear UTI after culture-sensitive appropriate antibiotic treatment
- ***Catheter associated UTI***: most likely secondary to meatal bacteria
- Sx: dysuria, urgency, frequency, hematuria, urinary incontinence, suprapubic pain
- Dx: positive urinalysis; urine culture with $> 10^2$ cfu/mL (straight catheterization); or $> 10^5$ cfu/mL (midstream clean-catch) and UTI symptoms
  - Rule out STDs, particular in young, sexually active men and women
- ***Asymptomatic bacteriuria***: positive urine culture (2 clean-catch or 1 catheterization) in an asymptomatic patient; usually does not require treatment
  - Antibiotic treatment: pregnant women (high risk for pyelonephritis); patients undergoing urologic procedures
  - No antibiotic treatment: diabetics, elderly, patients with indwelling catheters (colonization), spinal cord injury patients
    - Majority have E. coli without lipopolysaccharide (LPS) surface O-antigens; if antibiotics are administered the return of E. coli will likely have LPS O-antigens, thus increased virulence

Nitrite Negative UTI's

Pseudomonas and most gram-positive bacteria are nitrite negative; keep in mind for appropriate antibiotic selection

- Tx: trimethoprim- sulfamethoxazole (if resistance < 20%); ciprofloxacin; levofloxacin; nitrofurantoin (7 days); fosfomycin
  - Uncomplicated cystitis in women: 3-day antibiotic course
  - Uncomplicated cystitis in men: 7-day antibiotic course
  - Complicated cystitis – moderate illness: 10-14 days fluoroquinolone

  - o Complicated cystitis – severe illness: 14-21 days antibiotic course, starting with IV antibiotics until afebrile for 24 hours, then switching to oral antibiotics
    - * Relieve any outlet obstruction (e.g. Foley catheter)
  - o If uncomplicated reinfections, and a normal workup, consider either low-dose prophylaxis or self-start antibiotic therapy
    - * ***If vaginal atrophy***: intravaginal estrogen will reduce recurrent UTIs
  - o If uncomplicated reinfections related to coitus, consider postcoital prophylaxis
- Follow up:
  - o Post-antibiotic asymptomatic, young women need no further testing
  - o Symptomatic patients; elderly asymptomatic women; and men will need repeat urinalysis and culture after antibiotic treatment
  - o ***Complicated UTI/cystitis (all men), recurrent UTI, and reinfection UTI require further workup (e.g. cystoscopy and upper tract imaging)***

EMPHYSEMATOUS CYSTITIS

- Bladder infection by gas-producing bacteria that results in gas within the bladder wall
  - o Most common bacteria: E. coli and Klebsiella pneumoniae
- Majority of patients are ***diabetics***; bladder outlet obstruction is also a risk factor
- Sx: frequency, urgency, hematuria, suprapubic pain, rarely pneumaturia
- DDx: enterovesical fistula, genitourinary instrumentation (intraluminal bladder gas)
- Imaging: abdominal flat plate or pelvic CT scan shows air in the bladder wall
- Tx: catheter drainage (Foley vs. cystostomy), antibiotic, glucose control if diabetic

URINARY SCHISTOSOMIASIS (BILHARZIA)

- Schistosoma haematobium is a parasitic trematode (blood flukes)
- Most common in Africa
- Affinity for detrusor venous plexus; may lead to ureteral obstruction as well
- ***May lead to bladder cancer (vast majority are squamous cell carcinoma)***

SCHISTOSOMIASIS PRESENTATION

Schistosomiasis Form	**Description**
Inactive urinary	Nonviable eggs and dead trematodes; sandy patches on cystoscopy
Acute (Katayama Syndrome)	Serum sickness-like syndrome
Chronic	Hematuria; terminal dysuria; urgency, frequency

- Dx: urinary microbiology (eggs on microscopy); PCR assay
- Tx: ***Praziquantel***
    - See Bladder Tumors Chapter for bladder squamous cell carcinoma treatment

EOSINOPHILIC CYSTITIS

- Rare; inflammatory / allergic related bladder reaction with abundant eosinophils
- DDx: acute interstitial nephritis
- Tx: cystoscopy with resection; corticosteroids; anti-histamines; antibiotics

CANDIDURIA

- Fungal infection (yeast): Candida albicans, Candida krusei, Candida glabrata

- May have pyelonephritis, fungus ball/bezoars, renal abscess, ureteral obstruction, vulvovaginitis
- Common in patients with ***diabetes***, immunosuppression, or chronic catheters
- Dx: urinalysis – budding yeast, pseudohyphae, pyuria, hematuria; PCR
- Tx: remove or exchange catheter; stop antibiotics if possible; ***fluconazole***
  - Amphotericin B bladder irrigations
  - Adult: if asymptomatic, do not treat with antifungals
  - Infants: treat with fluconazole

Candida "-azole" Resistance

C albicans: susceptible

C. krusei and C. glabrata: resistance

| GENITALS |

See Sexual Transmitted Diseases Chapter for genital infections related to STDs and HIV.

FOURNIER'S GANGRENE

- Polymicrobial necrotizing fasciitis of the perineum and genitals
- Risks: ***diabetics, alcoholism***, immunosuppressed patients
- Etiology: urogenital vs. anorectal infection
- Dx: clinical diagnosis: crepitus (gas forming bacteria); variable progression, but may progress extremely rapidly; cellulitis; abscess; necrosis; sepsis; pain is variable as sensation may be blunted in diabetics
  - Patients many times report the infection "started as a pimple or spider bite"
  - Testicles are usually not involved, and may be spared

- Pathophysiology: ischemia with obliterative endarteritis; fascial necrosis
- Imaging: CT scan if atypical presentation or to determine extent of disease
- Tx: broad spectrum antibiotic therapy (gram positive/negative and anaerobic coverage), sepsis protocol, ***aggressive surgical debridement***
    - Strongly consider intraoperative "relook" within 24-48 hours for further debridement
    - Thigh pouches may be necessary to protect exposed testicles
    - Dakin's solution (sodium hypochlorite) may be used with wet-to-dry dressings
    - Consider negative pressure wound therapy (Wound VAC®) – reduces healing time once debridement is complete
- Prognosis: mortality rate of up to 1/3 of patients; majority are diabetics

Fournier's Gangrene

Colles, Dartos, and Scarpa's fascia are contiguous; allows for spread cranially to the clavicles and caudal to the tensor fascia lata

PROSTATITIS

- Most commonly intraprostatic ductal reflux
- Most commonly gram negative bacteria: E. coli (majority), pseudomonas, Klebsiella, enterobacter, serratia
    - Gram positive: enterococci (< 10%)
    - Other: chlamydia, ureaplasma, mycoplasma
- Prostate secretion pH increases (7.3 → 8.3)
- Sx: acute onset of perineal pain, LUTS, fever/chills, nausea/vomiting
- Dx: hot, boggy prostate on digital rectal exam; urine culture
- Tx: initially IV/IM antibiotics (penicillin + gentamicin; 2nd/3rd generation cephalosporin; or fluoroquinolone), then continue oral antibiotic for 14-28 days

  - If bladder outlet obstruction: CIC or cystostomy
  - If abscess: transurethral unroofing or percutaneous drainage
    - More common in diabetes, HIV, and other immunocompromised disease states

POST-PROSTATE BIOPSY INFECTION

- Increasing fluoroquinolone resistance has lead to increased infections
- Prophylaxis: fluoroquinolone; cephalosporin; aminoglycoside or aztreonam + metronidazole or clindamycin

ORCHITIS

- Testicular inflammation / infection
  - Acute: sudden onset pain / edema
  - Chronic: continued pain / edema for > 6 weeks
- Etiology:
  - Bacterial (most common) – E. coli, pseudomonas, gonorrhea, chlamydia
  - Viral: mumps virus (paramyxovirus)
  - Tuberculosis
  - Parasitic: Filariasis (see later in this chapter)
- ***Majority of patients have epididymo-orchitis; if orchitis alone, suspect viral etiology***
  - Young boys and older men: UTI-associated
  - Young sexually active men: STD-associated
- Dx: urinalysis, urine culture; possible STD testing
- Imaging: scrotal ultrasound - hyperemic flow; also to rule out torsion / malignancy
- Tx: anti-inflammatories, antipyretics, analgesics, antibiotics (fluoroquinolone)
  - If abscess → percutaneous or open surgical incision and drainage
- ***Scrotal pyocele***: infectious collection located between the visceral and parietal layers of the tunica vaginalis; associated with epididymo-orchitis

  - DDx: hydrocele (simple fluid), hematocele (trauma related), scrotal wall abscess (located within the cutaneous layers of the scrotum)
  - May evolve into Fournier's gangrene
  - Tx: surgical drainage, antibiotics

ORCHIALGIA

- Testicular pain
- Chronic is ≥ 3 months, and referred to as chronic scrotal content pain
- Tx: NSAIDs; if the patient responds to a spermatic cord block in the office, a **microdenervation** (genital branch of the genitofemoral and ilioinguinal nerves) of the spermatic cord may resolve the pain.
  - Last resort is orchiectomy.

EPIDIDYMITIS

- Infection is likely secondary to retrograde inflammation/infection from ejaculatory duct reflux of urine and/or bacteria
- Pediatric epididymitis is most commonly a viral etiology
  - Treat with ice pack and analgesics
- Acute bacterial epididymitis: UTI or STD-associated
- Sx: tenderness, edema
- Imaging: scrotal ultrasound - hyperemic flow_
- Tx: if < 35 years old → doxycycline or ceftriaxone
  - If > 35 years old → levofloxacin

Amiodarone

May cause a drug-induced epididymitis; treatment of choice is to decrease dose or stop medication

GENITAL FILARIASIS

- Lymphatic Filariasis
    - ***Wuchereria bancrofti*** (vast majority); Brugia malayi, Brugia timori
    - Parasite occludes the lymphatic system
    - Transmission vector = mosquito
    - Sx: variable presentation – fever, lymphangitis, lymphadenopathy, ***genital lymphedema***, hydrocele, elephantiasis
    - Dx: thick blood smear with ***Giemsa stain***
    - Imaging: ultrasound – ***filarial dance sign***
    - Tx: albendazole + diethylcarbamazine (DEC)
        - * If endemic Onchocerciasis, ivermectin in place of DEC.
- Onchocerciasis (River Blindness)
    - ***Onchocerca volvulus***
    - Filarial nematode that causes keratitis, and may lead to blindness
    - Transmission vector = blackfly; nearly exclusively found in Africa
    - Sx: palpable skin nodules; blindness; scrotal elephantiasis
    - Dx: skin snip biopsy; PCR
    - Tx: ***ivermectin*** (kills the larva); doxycycline (kills the adult worm)

CRYPTOCOCCOSIS

- Cryptococcus neoformans is a yeast that leads to pulmonary and CNS infections
- ***AIDS patients – prostate is a reservoir for relapsing cryptococcosis***
- Dx: ***India ink stain***
- Tx: fluconazole
    - If meningitis: Amphotericin B

| GENITOURINARY TUBERCULOSIS (TB) |

- ***Mycobacterium tuberculosis***
  - Aerobic, non-motile bacilli
  - Acid fast positive (red) on ***Ziehl-Neelsen stain***
  - ***Lowenstein–Jensen medium*** culture is difficult and may take several weeks; rarely used currently
- Infected by aerosolized infected droplets; most commonly spread to the genitourinary system via hematogenous route
- Approximately 1/3 of the world population has TB
  - Most common extrapulmonary TB: lymph node TB
  - 2nd most common extrapulmonary TB: genitourinary TB
- May result in active or latent infection
- Dx: Mantoux tuberculin skin test (aka PPD – purified protein derivative); interferon gamma release assay (IGRA; serum test)
  - ***Sterile pyuria***, microhematuria, frequency, urgency
  - Three consecutive early morning urine specimen for acid-fast staining and mycobacterium culture

GENITOURINARY TB IMAGE FINDINGS

TB Location	Image Findings
Renal	Renal calcifications (calcified caseating granulomas); ***moth eaten calyces*** (leads to papillary necrosis)
Ureter	***Stricture*** (most common in distal 1/3 of ureter); hydronephrosis
Bladder	Non-compliant, small bladder; bladder wall calcifications
Fallopian tubes	Most common female genital TB infection; salpingitis
Prostate/Seminal vesicles	Calcifications; caseating granulomas
Testes / Epididymis	Rarely involved; granulomatous epididymitis

- Tx: INH, Rifampin, Pyrazinamide x 2 months; then INH and Rifampin x 4 additional months
    - If INH resistance > 4%, add ethambutol or streptomycin for 1st two months
    - ***Isoniazid (INH):*** inhibits mycolic acid synthesis
        - If hepatotoxicity → stop medication
        - Side effect: peripheral neuropathy → vitamin B6 (Pyridoxine)
    - ***Rifampin***: inhibits RNA synthesis
        - Side effect: red urine
    - ***Pyrazinamide***: inhibits fatty acid synthetase I
    - ***Ethambutol:*** inhibits cell wall synthesis
        - Side effect: red-green visual disturbances
    - ***Streptomycin***: protein synthesis inhibitor
        - Side effect: ototoxicity, nephrotoxicity
- Nephrectomy indications: nonfunctional kidney; extensive disease;

coexisting renal cell carcinoma

- Distal ureteral stricture: TB medications x 3 weeks; if not improved, proceed with a 3-week steroid course; if still unimproved, proceed with ureteral dilation or re-implantation.
    - Consider a ureteral stent or percutaneous nephrostomy if obstructed
- Bladder augmentation indications: contracted, non-compliant bladder with adequate renal function

ANTIBIOTIC SUMMARY

Medication	Mechanism	G+	G-	SE/Notes
Beta-lactams (Penicillin)	Inhibit bacterial cell wall synthesis	++		Anaphylaxis; PCN G: IV/IM PCN V: oral
Cephalosporins* - 1st gen - 2nd gen - 3rd gen - 4th gen	Binds PCN binding proteins to inhibit bacterial cell wall synthesis	 +++ ++ + ++	 + ++ +++ +++	Only 1st gen has low cross-allergy with PCN allergies
Trimethoprim-sulfamethoxazole (TMP-SMX)	Inhibits folate TMP: inhibits dihydrofolate reductase SMX: Inhibits dihydropteroate synthetase (competes with PABA)	++ (MRSA)	++	SE: Stevens-Johnson syndrome, Kernicterus (infants), hemolytic anemia (if G6PD)
Quinolones*	Inhibit DNA gyrase & topoisomerase IV	++	+++	SE: tendonitis, tendon rupture, cartilage toxicity
Nitrofurantoin *	Bacterial flavoproteins convert to active products with multiple mechanisms of action	++ (urine)	++ (urine) lacks Proteus/ Pseudomonas coverage	SE: hemolytic anemia (if G6PD); Pulmonary fibrosis Poor systemic antibiotic
Vancomycin*	Inhibits peptidoglycan synthetase, stopping bacterial cell wall synthesis	+++		SE: Red Man Syndrome (given IV in < 1 hour)

Medication	Mechanism	G+	G-	SE/Notes
Aminoglycosides*	Inhibit mRNA 30S protein synthesis		+++	SE: ototoxicity, nephrotoxicity
Macrolides (e.g. erythromycin)	Inhibit mRNA 50S protein synthesis	++	+	SE: QT prolongation, inhibits CYP3a (increases many other drug levels)
Metronidazole*	Uptake by microbial cell and reduced to active metabolites	Effective against anaerobic bacteria and protozoa		SE: disulfiram-like reaction, metallic taste
Clindamycin	Binds 50S mRNA subunit and inhibits peptidyl transferase activity	Effective against gram positive and anaerobic bacteria		SE: pseudomembranous enterocolitis
Tetracyclines (e.g. doxycycline)	Binds 30S mRNA subunit; inhibits aminoacyl tRNA binding to the ribosome	++ (increasing resistance)	++ (good urine penetration)	SE: teeth yellowing, inhibit bone growth; Antacids interfere with absorption

** Indicates bactericidal antibiotics*

G+ = gram positive coverage, G- = gram negative coverage, Gen = generation, IV = intravenous, IM = intramuscular, PABA = para-aminobenzoic acid, PCN = penicillin, SE = side effects

NICHOLS PREOPERATIVE BOWEL PREPARATION

- Low residue diet 2-3 days prior surgery
- Mechanical bowel preparation and clear liquid diet 1-2 days prior surgery
- Day prior surgery Neomycin 1gm orally at 1pm
- Day prior surgery Erythromycin base 1gm at 2pm and 11pm
    - May substitute metronidazole for erythromycin (increased anaerobic coverage)

Preoperative bowel preparation has become controversial in more recent literature.

CHAPTER 30: HYDRONEPHROSIS

DEFINITIONS

- ***Hydronephrosis***: accumulation of urine within in the renal pelvis / calyces secondary to obstructed or decreased urine outflow
  - Acute vs. Chronic
  - Symptomatic vs. Asymptomatic
    - ***Dietl's Crisis***: acute renal colic secondary to diuresis with an underlying ureteropelvic junction obstruction
  - Obstructive
    - Urolithiasis
    - Stricture
    - Ureteropelvic junction obstruction
    - Ureteral tumor
    - Retroperitoneal fibrosis / lymphadenopathy / tumor
    - Bladder outlet obstruction (e.g. BPH, fecal impaction, posterior urethral valves, meatal stenosis)
    - Pregnancy (uterine compression of the ureter; possible progesterone contribution)
    - Ureteral blood clot / papillary necrosis
    - Iatrogenic (e.g. inadvertent suture ligation; postop fibrosis)
      - Post-vascular surgery obstruction
        - Up to ~ 30% have self-limited, asymptomatic hydronephrosis
        - Up to ~ 15% have permanent ureteral obstruction
        - Most commonly from retroperitoneal fibrosis

        - Ureterocele
        - Ureteral endometriosis
        - Cystocele
        - Pelvic lipomatosis
        - Nephroptosis
        - Retrocaval ureter
        - Ovarian vein syndrome (ureteral compression by a dilated ovarian vein)
        - Ureteral stent obstruction
    - Non-obstructive
        - Vesicoureteral reflux
        - Pyelonephritis (gram-negative bacterial endotoxin inhibits peristalsis)
        - Polyuria (e.g. diabetes insipidus, diuresis)
        - Megaureter
        - Megacalycosis
        - Extrarenal pelvis
        - Prune Belly syndrome
- ***Hydroureter***: accumulation of urine within the ureter secondary to obstructed or decreased urine outflow
    - Etiologies are similar to hydronephrosis, just more distal
- ***Pyelocaliectasis***: dilation of the renal pelvis and calyces
- ***Hydrocalyx***: dilation of a calyx

ACUTE PATHOPHYSIOLOGY OF URETERAL OBSTRUCTION

Obstruction Time (Hours)	Collecting System Pressure	Renal Blood Flow	GFR
0-2	↑	↑	Normal
3-4	↑	↓	↓
≥ 5	↓ / normal	↓	↓↓

- Acute, unilateral, ureteral obstruction-related hypertension is secondary to **hyperreninemia**
- Chronic ureteral obstruction leads to ***pyelovenous backflow*** of urine; there is also some tubulovenous and pyelolymphatic backflow

Renal Damage Reversibility

Reversible: first 2 weeks of obstruction

Irreversible: next 6-8 weeks of obstruction until complete renal destruction

WORKUP

See the Urologic Radiology chapter for specific details of imaging modalities.

- **Renal ultrasound**
  - Modality of choice for ***children, pregnant women, and routine screening***
  - ***Resistive index***: > 0.7 or a difference between kidneys > 0.1 indicates obstruction
  - ***Ureteral jets***: controversial; however, if absent, its an indirect sign of obstruction

ANTENATAL HYDRONEPHROSIS GRADING

Grade	Reflux Description
1	Slight renal pelvis splitting
2	Renal pelvis splitting with calyceal extension
3	Moderate pyelocaliectasis; normal parenchyma
4	Severe pyelocaliectasis; thinning parenchyma

- ***Retrograde pyelograms***: modality of choice for evaluation of upper tract collecting system, if contraindications to CT and MRI scans with IV contrast (e.g. contrast allergies and renal insufficiency)
    - Used in conjunction with renal ultrasound to evaluate the upper tract
- **CT Scan**
    - Non-contrast: modality of choice for ***urolithiasis***
    - Contrast ± delay images: modality of choice for ***upper tract tumors*** and ***incidental hydronephrosis workup*** (has replaced IVP as the gold standard)
        - * ***Contrast induced nephropathy***: post-IV contrast ATN that most commonly occurs with GFR < 60 mL/min/1.73m^2
- **Intravenous Pyelogram (Excretory Urography)**
    - Less radiation exposure than CT scans; however, decreased identification of hydronephrosis etiology
- **MRI Scan**
    - Modality of choice for ***endometriosis***
        - * ***Nephrogenic systemic fibrosis***: gadolinium induced systemic fibrosis that most commonly occurs with GFR < 30 mL/min/1.73m^2
- **MAG3**
    - Modality of choice for evaluation of ***renal function***; also identifies obstruction

MAG3 HALF-LIFE INTERPRETATION

Half-life (minutes)	**Interpretation**
< 10	Normal
10-20	Equivocal
> 20	Obstruction*

** False positives: severe renal pelvis dilation, renal insufficiency*

- **Ureteroscopy**
    - Direct ureteral visualization with possible biopsy and treatment (e.g. balloon dilation of a ureteral stricture)
- **Whitaker Test ("Ureteral Perfusion Challenge")**
    - Percutaneous nephrostomy tube insertion followed by a saline infusion at 10 mL/min, while monitoring renal pelvic and bladder pressure differences

WHITAKER TEST INTERPRETATION

Pressure Difference (cm H2O)	**Interpretation**
< 15	Normal
15-22	Equivocal*
> 22	Obstruction

** May increase infusion to 20 mL/min in equivocal cases*

- **Voiding cystourethrogram**
    - Modality of choice for ***vesicoureteral reflux***

VESICOURETERAL REFLUX GRADING

Grade	Reflux Description
1	Ureteral reflux ***only***
2	Ureteral ***and*** renal pelvis reflux ***without*** dilation
3	Ureteral and renal pelvis reflux with ***mild*** dilation
4	Ureteral and renal pelvis reflux with ***moderate*** dilation
5	Ureteral and renal pelvis reflux with ***severe*** dilation and tortuosity

MANAGEMENT

See specific diagnosis-related chapters for more detailed information.

- If ***no obstruction*** is present, consider observation with routine MAG3 screening / renal ultrasound
- If ***severe pain, UTI, acute renal insufficiency, sepsis, or immunocompromised,*** consider urgent ureteral stent or nephrostomy

INTRINSIC ETIOLOGY

- ***Urolithiasis***: consider ureteral stent, nephrostomy, ureteroscopic stone extraction
- ***Steinstrasse***: occurs in approximately 5% of postoperative extracorporeal shock wave lithotripsy (ESWL) patients
    - *o* If infected or obstructed: percutaneous nephrostomy (after insertion, many times the stones will spontaneously expulse)
    - *o* If non-infected and non-obstructed: ureteroscopy or further ESWL
- ***Upper tract tumor***: consider tumor ablation vs. nephroureterectomy
- ***UPJO*** or ***ureteral stricture***: consider MAG3 to determine renal function
    - *o* If split function is 10-40%, consider a pyeloplasty or ureteral stricture repair
    - *o* If < 10% split function AND pain, recurrent infection, HTN, or significant proteinuria, consider a nephrectomy

  - If < 10% split function AND pain-free, elderly, or poor surgical candidate, consider observation
- ***Ureterocele***: consider ureterocele ablation or partial nephrectomy if poor functioning renal unit
- ***Vesicoureteral reflux (VUR)*****:** VCUG findings direct treatment options - observation, prophylactic antibiotic, submucosal ureteral orifice injections, ureteral reimplant
  - See the Pediatric Urology Chapter for further VUR details
- ***Endometriosis***: consider GnRH agonist (e.g. Leuprolide), medroxyprogesterone or surgical resection with hysterectomy and bilateral salpingo-oophorectomy
- ***Nephroptosis***: (renal hypermobility), obtain MAG3 or IVP in standing and supine positions, and treat with a nephropexy
  - Dx: > 5cm renal caudal descent and > 10% decrease in renal split function
- ***Pyelonephritis***: treatment with appropriate antibiotic will resolve associated hydronephrosis.

Post-Surgical Surveillance

Consider re-imaging at 6 weeks and 3 months, then annually with renal ultrasound ± MAG3 or IVP

EXTRINSIC ETIOLOGY

- ***Retroperitoneal fibrosis***: consider glucocorticoid therapy for 6-24 months, chronic ureteral stent changes, or ureterolysis
- ***Cystocele***: consider pessary or cystocele repair
- ***Bladder outlet obstruction***: consider Foley catheter, suprapubic catheter, prostatic resection (e.g. TURP). May need urodynamics prior to surgery.
- ***Ovarian vein syndrome***: consider ovarian vein embolization or laparoscopic ligation
- ***Diabetes insipidus (DI)***: if central DI, treat with desmopressin (i.e. anti-diuretic hormone). If nephrogenic DI, treat with hydrochlorothiazide (paradoxical effect)

- ***Extrinsic tumor obstruction***: may try ureteral stent; however, these have a high failure rate. Consider percutaneous nephrostomy with primary tumor treatment as indicated.
- ***Pregnancy***: observation or ureteral stent if intractable pain

Extrinsic Hydronephrosis

In general, ureteral stents have a high failure rate (~50% at 1 year) when treating extrinsic hydronephrosis; nephrostomy tubes are better

STENTS

- Ureteral changes secondary to stents:
  - Hyperplasia / inflammation
  - Smooth muscle hypertrophy
  - Hydronephrosis
  - Decreased peristalsis
  - Vesicorenal reflux
  - Increased intrarenal pressure

CHAPTER 31: NEPHROLOGY

| NEPHRON FUNCTION |

GLOMERULAR FILTRATION RATE (GFR; ML/MIN)

- **Inulin clearance** = gold standard for calculating GFR because completely filtered by glomerulus without any renal tubular modification; however, it is time consuming
- **Creatinine clearance**: freely filtered by the glomerulus, but also ***secreted*** by the ***proximal tubule***; therefore, it ***overestimates*** the true GFR by 10-15%.
- **MDRD** (Modification of Diet in Renal Disease)
  - o **GFR** = 186 x serum $Cr^{-1.154}$ x $age^{-0.203}$

    x 0.742 (if female)

    x 1.21 (if African American)
  - o NOTE: for a constant creatinine (increasing Cr = decreasing GFR)
    - * GFR will decrease as you age because of decreased nephrons
    - * GFR is lower in females because they have less muscle mass
    - * GFR is higher in African Americans because of increased muscle mass
- **Cockcroft-Gault**
  - o **Creatinine clearance** = (140-age) x IBW(in kg) / (Cr x 72)

    x 0.85 (if female)

- NOTE: for a constant creatinine (increasing Cr = decreasing creatinine clearance)
  - Creatinine clearance will decrease with increasing age and females
  - Creatinine clearance will increase with increase with ideal body weight (IBW)

NEPHRON

- **Proximal tubules**
  - "Nephron workhorse" - reabsorbs majority of the electrolytes
  - Creatinine: 90% filtered / 10% secreted by proximal renal tubules
- **Loop of Henle**
  - Blood supply from ***vasa recta***
  - ***Countercurrent multiplier***
    - The loop starts and ends within the cortex, while the turn of the loop is within the medulla
    - Descending limb: permeable to water only (i.e. water leaves the limb), resulting in hypertonic urine within the limb
    - Thin ascending limb: permeable to solutes only (i.e. Na, Cl, K leave the limb), leads to a decreased hypertonicity of the urine within the limb
    - Thick ascending limb: active resorption via Na/K/2Cl symporter (i.e. more Na, Cl, K leave the limb) resulting in hypotonic urine within the limb
      - Site of action of ***loop diuretics*** (inhibits Na, Cl, K, Mg, Ca reabsorption)

NOTE: *Loop diuretics increase calcium within the urine; thiazides decrease calciuria.*

- **Distal tubules**
  - Main site of action for **Aldosterone**
  - Site of action of ***thiazide diuretics*** (inhibits NaCl reabsorption; decreases urinary calcium - important in urinary calculus disease)

- **Collecting Duct Cells**
    - Principal cells: secrete hydrogen into the urine
        - Aldosterone-dependent principle cells ***secrete K***
            - Sodium is reabsorbed while hydrogen and potassium are excreted
                - This mechanism is increased with aldosterone
        - Location of ***vasopressin (ADH) V2 receptors***
    - Intercalated cells: secrete hydrogen or bicarbonate into the urine
        - Alpha cells: secrete hydrogen via hydrogen-ATPase (up-regulated by aldosterone)
        - Beta cells: secretes bicarbonate via bicarbonate-chloride exchanger
- **Juxtaglomerular cells:** located within the wall of the ***afferent arteriole*** and produce / secrete renin.
- **Macula densa:** located in the wall of the ***distal tubule*** between the afferent and efferent arteriole
    - Senses decreases in sodium chloride, and then stimulates the juxtaglomerular cells via paracrine signals to increase renin

ELECTROLYTE ABSORPTION WITHIN THE NEPHRON*

Electrolyte	Proximal Tubule	Loop of Henle	Distal Tubule / Collecting Duct
Sodium	66%	25% - thick ascending (NaK / 2Cl symporter)	5% (aldosterone)
Potassium	66%	25% - thick ascending (NaK / 2Cl symporter)	5% (aldosterone)
Glucose	100%	---	---

Electrolyte	Proximal Tubule	Loop of Henle	Distal Tubule / Collecting Duct
Bicarbonate	90%	---	10%
Calcium	60%	25%	15% (PTH dependent)
Uric Acid	99% reabsorbed S1 50% secreted S2 40% reabsorbed S3 Net absorption: 90%	---	---

** Percentages are approximate to aid with memorization*

- **Hyponatremia**
  - o Rule out ***SIADH*** (syndrome of inappropriate antidiuretic hormone), especially with small cell carcinoma present
    - * SIADH: normal BUN/Creatinine with low serum uric acid
      - Hyponatremia, increased urine osmolarity, urine sodium > 40 mEq/L
  - o High serum uric acid conditions and pre-renal kidney injury
    - * Decreased intravascular volume: Addison's disease (adrenal failure), diarrhea
    - * Volume overload states: CHF, cirrhosis
  - o Do not correct too quickly → ***central pontine myelinolysis***
- **Hypernatremia**: do not correct quickly → ***cerebral edema***
  - o Rule out diabetes insipidus (hypovolemic hypernatremia)
- **Hypokalemia**
  - o Usually secondary to GI or GU losses, diuretics, laxatives
  - o Cardiac changes: QT prolongation, ST depression, T-wave flattens, U-waves
  - o Tx: potassium replacement

- **Hyperkalemia**
    - Cardiac changes: QT shortening, peaked T-waves
    - Tx: insulin, bicarbonate, sodium polystyrene sulfonate (Kayexalate®); calcium gluconate or calcium chloride (cardiac stabilization)

Hypokalemia on an EKG

Appears like the EKG has been pulled like a string, which results in an flat / stretched out EKG

| RENIN ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS) |

RENIN

- Secreted from juxtaglomerular cells in response to:
    - Decreased renal perfusion (hypoperfusion)
    - Glomerular, ***afferent arteriolar resistance*** (regulates renal perfusion)
    - Beta-1 adrenergic receptors (sympathetic stimulation)
    - Macula densa stimulation due to decreased sodium
- Physiologically inert
- Converts Angiotensinogen (from liver) to Angiotensin I
- Reninoma - usually benign, HTN with excessive renin and secondary hyperaldosteronism

ANGIOTENSIN I

- Physiologically inert
- ***Angiotensin Converting Enzyme*** (ACE) converts Angiotensin I to Angiotensin II (vasoconstrictor)
    - ACE also degrades bradykinin (vasodilator)
    - ACE is classical produced in the lungs; however, endothelial cells also play role

ANGIOTENSIN II

- Potent ***vasoconstrictor***
    - Responsible for renovascular HTN (2 kidneys, 1 clip)
- Stimulates the zona glomerulosa of the adrenal gland to secrete ***aldosterone***
- Stimulates the posterior pituitary gland to release ***ADH***
- Increases ***thirst*** in attempt to increase extracellular volume
- Stimulates ***cardiovascular hypertrophy***
- Two Angiotensin II receptors: ***AT1*** (majority of activity) and AT2 (unclear activity)

ALDOSTERONE

- Increases ***distal tubule reabsorption of sodium*** (thus water) in exchange for potassium and hydrogen secretion
- Conn's syndrome - hyperaldosteronism secondary to a functional adenoma or bilateral idiopathic hyperaldosteronism

ANTIDIURETIC HORMONE (VASOPRESSIN)

- Released from the ***posterior pituitary gland***
- ***Vasoconstriction*** via ***V1 receptors*** on vascular smooth muscle
- Increased renal ***water absorption*** via ***V2 receptors*** on the principal cells that stimulate ***aquaporins*** within the collecting ducts

| ACUTE KIDNEY INJURY |

- ***Acute kidney injury (AKI)***: rapid, usually reversible, decline in GFR
- Categories: Pre-renal, Intrinsic, Post-renal
    - ***Non-oliguric***: urine output is > 400 cc/day
    - ***Oliguric***: urine output is 100-400 cc/day
    - ***Anuric***: urine output is < 100 cc/day
- ***Acute renal failure (ARF)***: AKI that results in a need for dialysis

Trimethoprim – "Pseudo-AKI"

Inhibits proximal renal tubular creatinine secretion, which leads to an increase in serum creatinine, but GFR is unaffected

| PRE-RENAL AKI (70%) |

- AKI as a result of renal hypoperfusion
- Etiology: ***intravascular volume depletion (i.e. dehydration)***, reduced cardiac output, systemic vasodilation, renal vascular hypoperfusion
- RAAS is activated in an attempt to expand intravascular volume and increase renal perfusion
- Lab: classically, ratio of ***BUN:creatinine is > 20:1***
    - This ratio occurs secondary to increased urea reabsorption and decreased urea secretion in an attempt to expand the intravascular volume. This is done without altering creatinine reabsorption
- ***Fractional excretion of sodium (FENa) < 1***: the nephron avidly reabsorbs sodium
- ***Elevated urine specific gravity***: the nephron retains water avidly, thus higher concentration of urine solutes, ***elevated urine osmolality***, and a low urine output

| INTRINSIC AKI (25%) |

- AKI as a result of renal parenchymal injury
- Etiology: ***acute tubular necrosis (ATN)***, ischemia, acute interstitial nephritis, trauma, vasculitis, renal transplant rejection, glomerulopathies

ATN

- ***Proximal tubule*** injury/death secondary to ischemia or toxicity, which does not allow tubules to reabsorb or secrete electrolytes
    - Think of the nephron being a solid pipe with no exchanging of molecules, as the pours are clogged with dead tubule cells
    - ***Urine osmolality*** is ***isotonic*** because the kidney is unable to concentrate nor dilute the urine, thus the ***urine specific gravity*** is ***isosthenuric*** (1.010; same as protein-free serum plasma)
    - Hypokalemia: unable to reabsorb K
- **Phase 1: Initiation** - onset of AKI
- **Phase 2: Maintenance** - continued AKI, usually 1-2 weeks
- **Phase 3: Recovery** - resolution of AKI with return of tubular function
    - 99% will recover by 6 weeks
- Lab: minimal proteinuria (< 1gm / day; if more, consider injury to glomerulus)
    - *FENa > 2* - unable to reabsorb (i.e. salvage) sodium in the proximal tubules
    - ***Muddy brown granular casts***
- Mortality may be up to 50% in surgical patients, and 33% in medical patients

AMINOGLYCOSIDES NEPHROPATHY

- Aminoglycosides result in direct toxic effects on the ***proximal tubule***, as well as renal vasoconstriction
- Renal function decreases at approximately ***5 days of treatment***
- ***Single daily dosing*** is recommended over the classic TID administration because of the saturation phenomenon (once the proximal tubule is saturated, no further injury occurs from the increased single dose; rather reaching the saturation point multiple times will result in more injury)
    - e.g. Gentamicin 7 mg/kg/day
    - Utilizes concentration-dependent killing method
    - If elevated trough level (low point) just prior to re-dosing, then maintain dosage, but increase the time interval between doses

CONTRAST INDUCED NEPHROPATHY

- Etiology is unclear; however, likely a similar effect as aminoglycosides
- Renal function decreases in approximately ***24-72 hours after contrast administered***
- Prevention: best method is ***adequate hydration***; N-acetylcysteine is an antioxidant which may be beneficial

ACUTE INTERSTITIAL NEPHRITIS

- AKI associated with acute inflammation and edema of the ***renal interstitium***
- Etiology: vast majority are ***drug hypersensitivities*** (particularly ***beta-lactam antibiotics***), diuretics, NSAIDs, infection, autoimmune reactions
- Classic triad (rare): fever, rash, arthralgia
    - Ranges from asymptomatic to oliguric renal failure
- ***Eosinophilia*** is common but not pathognomonic; diagnosis proven with biopsy if needed
- Tx: withdraw offending agent, corticosteroids are controversial

PAPILLARY NECROSIS

- Renal ischemia leading to necrosis of the medullary pyramids and papillae
- **Etiology Mnemonic** – “AD SPORT C”
    - Analgesic abuse
    - Diabetes mellitus
    - Sickle-cell disease
    - Pyelonephritis
    - Obstruction
    - Renal vein thrombosis
    - Tuberculosis (renal)
    - Cirrhosis
- Tx: treat underlying etiology; ureteral stent or nephrostomy drainage if obstruction

Papillary Necrosis

Impairs medullary antibiotic concentrating ability, thus decreases ability to sterilize the urine

TUMOR LYSIS SYNDROME (TLS)

- Metabolic abnormalities, including acute renal failure, secondary to rapid lysis of neoplastic cells by chemotherapeutic agents
- Dx: laboratory studies; renal ultrasound to rule out hydronephrosis (i.e. obstruction)
- Tx: aggressive hydration and diuresis; consider allopurinol to prevent TLS

TUMOR LYSIS SYNDROME METABOLIC ABNORMALITIES

Abnormality	Etiology	Manifestation
Hyperuricosemia	High purine turnover	Uric acid crystal nephropathy
Hyperphosphatemia	Intracellular release of phosphate	Precipitation with calcium obstructs renal tubules, nephrocalcinosis
Hypocalcemia	Precipitates with phosphate	Muscle cramps, tetany, cardiac arrhythmias
Hyperkalemia	Intracellular release and renal failure	Muscle cramps, paresthesias, cardiac arrhythmias, death

| POST-RENAL AKI (5%) |

- AKI as a result of genitourinary tract obstruction (anywhere from the collecting system to the urethral meatus)
- Etiology: renal pelvis, ureter, bladder outlet or urethral obstruction from many possibilities including tumors, fibrosis, radiation, inflammation, hematoma, calculi, strictures, edema, BPH, neurogenic bladder, medication effect, infection, papillary necrosis (sterile pyuria with WBC casts)
- Tx: remove obstruction, ureteral stent, percutaneous nephrostomy, anti-inflammatory, and/or Foley catheter
- Monitor for ***Post-obstructive Diuresis***
  - Physiologic diuresis occurring after removal of obstruction
    - ***Output > 200 cc / hour after relieving > 1 liter of urinary retention***
  - Usually self-limited once excess free water and solutes are eliminated; however, may become pathologic and lead to marked natriuresis and electrolyte wasting
  - Allow the patient to have free access to fluids if adequate cognition to avoid prolonging diuresis; if unable, then replace with 0.45% normal saline at a rate 1/2 of the hourly urine output
  - Monitor serum electrolytes routinely and urine osmolarity

SUMMARY OF LAB FINDINGS IN PRE-RENAL AKI VERSUS ATN

Index	Pre-Renal AKI	ATN
FENa [(UNa/PNa) / (UCr/PCr)] × 100	< 1%	> 2%
Urine sodium concentration	< 20	> 40
Urine Cr: Plasma Cr ratio	> 40	< 20
Urine specific gravity	> 1.018	1.010 (Isosthenuria)
Urine osmolality	> 500	300 (isotonic)
Plasma blood urea nitrogen/creatinine ratio	> 20	< 10-15
Urine sediment	Hyaline casts	Muddy brown granular casts

| CHRONIC KIDNEY DISEASE (CKD) |

- Renal damage or GFR < 60 mL for at least three consecutive months
- End-Stage Renal Disease (ESRD) results in the patient necessitating renal replacement therapy (i.e. dialysis)

CHRONIC RENAL DISEASE CLASSIFICATION

Stage	GFR (mL / min / 1.73m2)
1	≥ 90*
2	60-89
3	30-59

Stage	**GFR (mL / min / 1.73m2)**
4	15-29
5 (ESRD)	< 15

* *Normal function currently but known underlying renal disease*

CO-MORBIDITIES ASSOCIATED WITH ESRD

- **Secondary hyperparathyroidism** (elevated PTH)
  - o PTH usually increases calcium resorption in the renal ***distal*** tubule, and this pathway is inhibited
    - * Note: calcium resorption in the renal proximal tubule is not stimulated by PTH
  - o Vitamin D deficiency because inability to convert 25 to 1-25 (active vitamin D) in the kidney
    - * Vitamin D normally increases small bowel calcium absorption
  - o ***Renal osteodystrophy***: bone demineralization
  - o May also cause insulin resistance
  - o Tx: Calcitonin (PTH antagonist) and Calcitriol (active vitamin D3)

Stimulation for PTH Release

Decreased calcium; increased phosphate; increased vitamin D3 (calcitriol)

- **Hyperphosphatemia**
  - o Ineffective renal clearance leads to increase phosphate levels
  - o PTH increases the amount of phosphate from bone resorption
    - * Normally PTH stimulates renal loss of phosphate, but unable to filter in ESRD

  - Tx: Phosphate binders at meals
- **Hyperprolactinemia**
  - Results in decreased LH/FSH
    - Women: galactorrhea, infertility, amenorrhea
    - Men: ED, decreased libido, decreased testosterone
      - Likely ok to replace testosterone, but not promising results
- **Metabolic acidosis**
  - Inability to clear acid
- **Subclinical hypothyroidism**
  - Tx: Levothyroxine prn
- **Growth hormone resistance**
- **Anemia of chronic disease**
  - No/low erythropoietin
  - Tx: Epoetin alfa
- **Hyperkalemia**
  - Most common cause is poor diet
- **Hypercoagulability**
  - Loss of natural anticoagulants (antithrombin III, protein C & S) via urine due to associated nephrotic state
  - Hyperhomocysteinemia
  - If lupus induced ESRD - antiphospholipid antibodies and anti-apolipoprotein H antibodies
- **Abnormal bleeding times**
  - Poor platelet aggregation
  - Temporary reversal seen with desmopressin, cryoprecipitate, conjugated estrogens, erythropoietin or dialysis
  - Platelet transfusion is usually not helpful because aggregation does not improve with more platelets

RENAL MASS ASSOCIATION WITH ESRD

- 80% of dialysis patients have ***acquired renal cystic disease***
  - Approximately 2% will develop renal cell carcinoma
- Renal ultrasound annually after the 5th year of dialysis

NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

- Systemic fibrosis occurring after administration of gadolinium in dialysis patients
- Gadolinium is relative contraindication if ***GFR < 30*** $mL/min/1.73m^2$ because of the increased risk for NSF

| NEPHRITIS AND NEPHROPATHY |

NEPHRITIC SYNDROME

- UA: hematuria, proteinuria, dysmorphic RBCs/casts
- Usually mild to moderate proteinuria, HTN, edema
- Renal insufficiency is common
  - Most common: rapidly progressive glomerulonephritis (RPGN)
- Categories
  1. Antigen-antibody immune complex (e.g. IgA nephropathy, PSAG)
  2. Antibody against basement membrane (e.g. Goodpasture)
  3. Pauci-immune (Churg-Strauss)

IGA NEPHROPATHY (BERGER'S DISEASE)

- ***Recurrent gross hematuria in young adults after an upper respiratory infection or exercise***
  - Occurs while acutely ill
- May have flank pain from clot colic
- 25% develop renal insufficiency
- Lab: renal biopsy: ***renal mesangial cell deposition of IgA***

POST-STREPTOCOCCAL ACUTE GLOMERULONEPHRITIS (PSAG)

- ***Gross hematuria after a streptococcal illness***
- Will have a ***latency period*** prior gross hematuria
    - Strep throat: 7 days
    - Pyoderma: 21-30 days
- Lab: ***anti-streptolysin-O positive***, streptozyme titer and ***low serum complement C3/C4***
- Gross hematuria occurs while acutely ill in IgA nephropathy, while a latency period occurs with PSAG

RENAL GLOMERULONEPHRITIS TESTS

- ***ANCA (anti-neutrophil cytoplasmic antibodies)***
    - Necrotizing systemic vasculitis
    - Wegener's granulomatosis (hemoptysis, epistaxis, RPGN)
    - Polyarteritis nodosa
- ***Anti-GBM Abs (anti-glomerular basement membrane antibodies)***
    - Goodpasture Syndrome (dry cough, hemoptysis, RPGN)
        - Type 2 hypersensitivity reaction against pulmonary and renal collagen type 4

NEPHROTIC SYNDROME

- UA: severe proteinuria (> 3.5gm; predominant feature), usually without RBCs/casts
- Usually edema, hypercholesterolemia, hypoalbuminemia
    - More indolent process than nephritic syndrome

URINE PROTEIN-CREATININE (P:CR) RATIO

- Rough assessment of proteinuria in lieu of 24 hour urine
    - Use first morning void
- Normal adult protein excretion / day = 30-130mg
- Normal adult creatinine excretion / day = 1gm
    - Therefore ***Urine P:Cr < 0.2 is normal***
    - Urine P:Cr > 3 suggest nephrotic proteinuria

  - If Cr excretion per day is > 1 (i.e. large muscle mass) then not good test to utilize

| ACID / BASE |

DETERMINING ACID / BASE STATUS

DETERMINE SERUM PH STATUS

- Acidemia pH < 7.35; alkalemia pH > 7.45
- Primary abnormality lies in direction of pH disorder, body does not overcompensate

DETERMINE IF ANION GAP = NA - CL - HCO3

- Normal 8-12

DEGREE OF COMPENSATION / TWO DISORDERS

- Metabolic Acidosis - Winters formula determines if there is a respiratory component by calculating the expected $pCO2 = 1.5 \times HCO3 + 8 \pm 2$
  - If measured pCO2 > expected pCO2: respiratory acidosis
  - If measure pCO2 < expected pCO2: respiratory alkalosis
- Metabolic Alkalosis
  - Increase in pCO2 = 0.6 * (increase in HCO3)
- Respiratory Acidosis
  - Acute: every 10 point increase of pCO2, HCO increases by 1
  - Chronic: every 10 point increase of pCO2, HCO increases by 4
- Respiratory Alkalosis
  - Acute: every 10 point decrease pCO2, HCO decreases by 2
  - Chronic: every 10 point decrease pCO2, HCO decreases by 5

DETERMINE IF TRIPLE DISORDER WITH DELTA GAP = DELTA ANION GAP / DELTA HCO

- DG < 1: Anion Gap + Non-Anion Gap Metabolic acidosis

- DG = 1 Only One Metabolic Disturbance
- DG > 1.5-2: Anion Gap Metabolic Acidosis + Metabolic alkalosis
    - Delta = difference of measured value and normal value

ACID / BASE SUMMARY

Disorder	pH	HCO3	pCO2
Normal	7.40	24	40
Metabolic Acidosis	↓	↓	↓
Metabolic Alkalosis	↑	↑	↑
Respiratory Acidosis	↓	↑	↑
Respiratory Alkalosis	↑	↓	↓

Lightly shaded boxes represent normal compensatory reactions.

ANION GAPPED METABOLIC ACIDOSIS

- Anion gap = Na - Cl - HCO3
    - Normal is 8-12, which accounts for minor electrolytes and albumin
    - The anion gap increases when other substances below are present during acidosis
        - **M**ethanol (may cause optic nerve damage and blindness)
        - **U**remia (more common in CKD than ARF)
        - **D**iabetic / alcoholic / starvation ketoacidosis
        - **P**araldehyde
        - **I**soniazid / Iron
        - **L**actic acid (commonly seen in sepsis)
        - **E**thylene glycol (alcoholics may ingest)
            - ***Fomepizole*** - antidote for methanol and ethylene glycol overdoses
        - **S**alicylates

MUDPILES Mnemonic

Anion gapped metabolic acidosis

NON-ANION GAPPED (HYPERCHLOREMIC) METABOLIC ACIDOSIS

- Anion gap is within the normal range; however, chloride is elevated
- **H**yperalimentation (insufficient HCO3)
- **A**cetazolamide (inhibits proximal tubule reabsorption of HCO3)
- **R**TA/Renal insufficiency (inability to clear acidosis in urine)
- **D**iarrhea (stool loses HCO3, K, Na relatively > Cl)
- **U**reteroenterostomy (Cl is absorbed; HCO3 binds acidic urine & excreted)
- **P**ancreatic fistula

HARDUP Mnemonic

Non-anion gapped metabolic acidosis

METABOLIC ALKALOSIS

- **Chloride sensitive (Contraction Alkalosis; low urinary chloride, < 10 mmol/L)**
  - Etiology: vomiting, gastric suction / lavage, diuretic use, posthypercapnia
  - Tx: ***saline*** infusion (volume depletion)
- **Chloride resistant (high urine chloride, > 20 mmol/L)**
  - Etiology: excess mineralocorticoid activity, primary hyperaldosteronism, licorice (glycyrrhizin), exogenous steroids, Cushing's disease, Bartter's syndrome, excessive alkali administration

NOTE: *aldosterone not only causes loss of potassium but hydrogen as well*

- Tx: ***potassium-sparing diuretic***
  - * Saline resistant because current state of volume expansion and hypokalemia

CHAPTER 32: RENOVASCULAR HYPERTENSION

DEFINITION

- ***Hypertension (HTN):*** > 140/90 mmHg
    - If renal disease or diabetes: 130/80
- ***Renovascular HTN (RVH):*** HTN due to renal arterial lesion, and the HTN resolves with correction of the offending lesion or nephrectomy
    - Renal artery stenosis must be functionally significant
    - 1-5% of all hypertensive patients (most common secondary etiology of HTN)
- Classifications
    - ***Atherosclerosis obliterans – 90%***
    - ***Fibromuscular dysplasia – ~ 10%***

2 KIDNEYS, 1 CLIP

- Kidneys fight each other to negate each other's effect
    - Unilateral renin from ischemic kidney
    - Contralateral suppression renin release from normal kidney
    - Sodium retention from ischemic kidney
    - Sodium excretion from contralateral kidney
- RVH from ***Angiotensin II***
    - ***Vasoconstriction*** (euvolemia)
- Tx: ***ACE inhibitors***

1 KIDNEY, 1 CLIP OR 2 KIDNEYS, 2 CLIPS

- RVH from ***Aldosterone*** → increased volume, sodium
  - o Natriuresis can not occur in normal kidney
  - o Stenotic kidney avidly reabsorbs sodium and fluid
  - o Once enough fluid is retained to maintain adequate renal perfusion pressure the renin returns to normal levels
- May be seen as post-nephrectomy hypertension
- ACE inhibitors do not help
- Tx: ***diuretic***

GOLDBLATT KIDNEY MODEL

Kidney/Clip Model	Renin	Pathophysiology	Treatment
2 kidneys, 1 clip	↑	Angiotensin II	ACE inhibitor
1 kidney, 1 clip	Normal	Volume overload	Diuretic

| ATHEROSCLEROSIS (ASO) |

- Eccentric (intimal) plaque of the ***renal artery proximal 1/3***
- ***Progresses to obstruction 40% of the time*** (usually occurs within 2 years)
- ASO is a systemic disease, and may also lead to end-stage renal disease (ESRD)
- Tx: medical therapy
  - o If refractory to medical therapy or ischemic nephropathy: consider surgery / Percutaneous Transluminal Angioplasty (PTA); however, difficult to determine if patient will benefit from a vascular procedure

| FIBROMUSCULAR DYSPLASIA (FMD) |

- Categorized by the predominant arterial layer involved: intima, media, or adventitia

MEDIAL FIBROPLASIA

- 75-80% of FMD
- Women 25-50 years old
- Bilateral renal arteries have muscle replaced by collagen in a series of rings
    - ***Usually does not progress***
- ***"String of beads" on angiogram – distal 2/3 of renal artery***
- Associated with Ehlers-Danlos Syndrome
- Tx: medical treatment
    - Refractory = PTA

PERIMEDIAL FIBROPLASIA

- 10-15% of FMD
- Young women 15-30 years old
- Outer border of media tight collagen ring (external elastic lamina)
- ***Progresses***
- Looks like beading, but no bead in front of the normal segment on angiogram
- Tx: non-operative due to ***collateral circulation***

INTIMAL FIBROPLASIA

- 10% of FMD
- Kids / young adults
- Proximal focal stenosis with collagen in the internal elastic lamina which may result in medial dissection
- **Progresses**
- Tx: PTA

FIBROMUSCULAR HYPERPLASIA (AKA ADVENTITIAL OR PERI-ARTERIAL)

- 2-3% of FMD (rarest form)
- Kids, young adults
- Hyperplasia of smooth muscle cells
- **Progressive**
- Tx: surgical revascularization

SUMMARY OF FIBROMUSCULAR DYSPLASIA

FMD	FMD %	Progression	Treatment
Medial Fibroplasia	75-80%	No	Medical
Perimedial Fibroplasia	10-15%	Yes	Medical
Intimal Fibroplasia	10%	Yes	PTA
Fibromuscular Hyperplasia	2-3%	Yes	Surgical revascularization

| RENAL INJURY |

ISCHEMIC NEPHROPATHY

- Renal artery stenosis may lead to decreased renal function with or without HTN
- The ***medulla is most sensitive to ischemia*** due to "last in line" to receive blood
- Bilateral severe stenosis (***> 70% stenosis***); or stenosis of a **solitary** kidney leads to ischemic nephropathy
- Results in ~ 10% of new ESRD
- Kidney needs only 10% of its blood flow to maintain its O2 requirement

RENAL CHOLESTEROL EMBOLISM

- Seen in older patients with HTN and severe aortic ASO
- Etiology: ***angiography***, thrombolytics (the plaque ruptures and then showers cholesterol emboli)
- ***Blue dots on toes/finger***s, may lead to renal dysfunction
- Tx: remove inciting trauma, cessation of anticoagulation, control HTN, dialysis prn

| RVH SCREENING |

CONSIDER SCREENING:

- Hypertension onset < 30 years old (FMD) or > 50 years old (ASO)
- Elevated creatinine shortly after starting an ACE inhibitor
- Hypertension with asymmetric renal size
- Severe, refractory hypertension or sudden worsening of hypertension
- Abdominal bruit with hypertension
- Hypertension with recurrent flash pulmonary edema

TESTING

- ***Gold standard = angiography*** (invasive, so usually other screening tests are used)
- Captopril MAG3 has sensitivity / specificity > 90% (function testing)
- Duplex ultrasound = anatomic test
  - Normal peak systolic velocity = 100 +/- 25
  - Renal artery stenosis: ***> 180 cm/sec peak systolic velocity***
  - Renal:Aortic ratio > 3.5 = 60% stenosis
    - Sensitivity/specificity 98%
- Magnetic Resonance Arteriogram (MRA) is a little better than duplex ultrasound

ISCHEMIC NEPHROPATHY

- Requires anatomic scan because may not have HTN
  - Strong suspicion = ***angiogram***
  - Mild/mod suspicion = duplex ultrasound, MRA, CT Angiogram
    - If any of these are positive = angiogram

RENAL VASCULAR HYPERTENSION (RVH)

- Requires functional scan
  - Strong suspicion = ***angiogram***
  - Mild/mod suspicion = captopril renography
    - If positive = angiogram
    - If study unsatisfactory = duplex ultrasound

RENAL RESISTIVE INDEX (RI)

- RI = (systolic – diastolic) / systolic
  - Normal RI = 0.6
  - ***Renal obstruction: RI > 0.7*** or RI difference between kidneys > 0.1
- If ***vessel narrowing*** (e.g. RAS) the peak systolic flow velocity decreases, while the peak diastolic increases, resulting in a ***decreased RI***.
- ***Elevated RI***: transplant rejection, obstruction, ATN, pyelonephritis, severe hypotension, or an acute vascular event (e.g. renal vein thrombosis).

| SURGICAL INTERVENTION |

SURGICAL BENEFIT

- **Possible (i.e. PTA)**: ***resistive index < 0.80*** on duplex; ***Cr < 4***; ***kidney > 7 cm***; lateralization of renin on sampling; > 75% occlusion solitary kidney or bilaterally, recurrent pulmonary edema
- **Unlikely (i.e. medical treatment - dialysis - transplant)**: ***medial***

fibroplasia, resistive index > 0.80, Cr > 4, no lateralization, nonfunctional kidney on renal scan, ASO without nephropathy

- Do not treat ASO with surgery unless failing 3 antihypertensive medications

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA)

- Fracture of the atherosclerotic plaque and stretching of the arterial wall that results in tearing of media and adventitia
- Complications: decreased renal function due to IV contrast; intimal dissection or thrombosis of renal artery
- If the plaque starts at the ostium of renal artery (i.e. aorta), then PTA results are decreased
- Takayasu's arteritis: good results
    - o If fails = auto-transplant artery

RENAL ARTERY SURGERY

- Indications: failed PTA ± stent, complicated aortic/renal disease, fibromuscular hyperplasia, renal artery aneurysm, ischemic nephropathy
- Options: renal artery bypass, endarterectomy, or nephrectomy (nonfunctional kidney)
- Medial fibroplasia reduces success rates (progressive form of FMD)
- Mortality: 5-10%

SURGICAL REVASCULARIZATION SUCCESS RATES*

	Cure	Improved	Failure
FMD	60%	30%	10%
ASO	30%	60%	10%

* *Overall mortality = 3% (PTA) and 5-10% (surgical); all numbers are approximations*

| MISCELLANEOUS |

RENAL ARTERY ANEURYSMS

- Fairly uncommon incidence (< 0.3%)
- Often associated with hypertension (55%); many are silent
- Types: ***saccular*** (most common; > 90%), fusiform, dissecting and arteriovenous
- May have abdominal bruit with palpable abdominal mass near the kidney
- Tx: ***< 1.5 cm conservative management*** such as sodium restriction, weight loss, and antihypertensives
    - o ***Surgical excision or endovascular treatment if:***
        - * > 2.5 cm; uncontrolled HTN
        - * > 1cm in young female in child-bearing years
        - * Aneurysmal growth
        - * Concomitant fistula
    - o If endovascular stent is utilized, will likely need long-term anti-coagulation, so not a great option for young patients
- Rupture is uncommon
    - o Renal artery aneurysms in women of childbearing age have an increased risk of rupture and require more aggressive treatment
- Completely calcified renal artery aneurysms tend to be stable and unlikely to rupture

PAGE KIDNEY

- Subcapsular/perirenal compression yields an increase in ipsilateral renin secretion and a contralateral renin suppression
- ***"2 kidney, 1 clip" like***
    - o Increased ***angiotensin*** leading to ***vasoconstriction***

NEUROFIBROMATOSIS (VON RECKLINGHAUSEN DISEASE)

- *Renal artery stenosis* is the most common cause of HTN in these patients secondary to invasion of arterial intima by neural tissue
- ***Rare, but pheochromocytoma may be the etiology of HTN***

CHAPTER 33: RENAL TRANSPLANT

DEFINITIONS

- ***Autograft***: tissue transplant from one site of the body to another in the same patient (e.g. skin graft)
- ***Isograft***: tissue transplant between genetically identical patients (e.g. renal transplant between monozygotic twins)
- ***Allograft***: tissue transplant between genetically dissimilar patients in the same species (e.g. donor renal transplant)
- ***Xenograft***: tissue transplant between individuals in different species (e.g. porcine skin grafted on human burn victim)
- ***Orthotopic graft***: placement of an organ in the normal anatomical position (e.g. cardiac transplant)
- ***Heterotopic graft***: placement of an organ at a site different from the normal anatomic position (e.g. renal transplant)

ABO BLOOD GROUP COMPATIBILITY *

ABO Group	Antigen	Serum Antibody	Blood Compatibility
O	---	Anti-A Anti-B	O
A	A	Anti-B	A, O
B	B	Anti-A	B, O
AB	A and B	---	AB, A, B, O

- If incompatibility occurs, then antibody-mediated killing of the endothelium occurs. The result is thrombosis and organ necrosis, as seen in ***hyperacute rejection***.

HISTOCOMPATIBILITY

- ***Haplotype***: group of alleles for different genes on a chromosome that are in close proximity, and subsequently they are inherited as a group
  - Better match: 2-haplotype > 1-haplotype > 0-haplotype
- ***Major histocompatibility complex (MHC)***: encodes glycoproteins expressed on almost all cells surfaces, which allows the immune system to distinguish between self and non-self; this determines histocompatibility
- ***Human Leukocyte Antigen (HLA)*** = MHC in humans is on ***chromosome 6***
  - **MHC class 1: HLA - A, B, or C**
    - Cellular immunity: on nearly all cells (not on sperm)
    - Attracts ***CD8 cells*** (cytotoxic or killer T cells)
    - Testing: complement-dependent microcytotoxicity
  - **MHC class 2: HLA D, Dr, Dq, or Dp**
    - Antigens found on B-lymphocytes and antigen presenting cells (APC)
    - Presents antigen to ***CD4 cells*** (helper T-cells)
    - Testing: mixed lymphocyte culture (MLC)
      - Takes 5-7 days, not useful in cadaveric donors

| PREOPERATIVE SCREENING |

- Screen for ***cardiovascular disease,*** which is the **leading cause of death after renal transplantation**
- **Absolute contraindications**: untreated malignancy and active infection

- **Relative contraindications**
    - Infection: osteomyelitis, diabetic foot ulcers, TB
        - Note: Hepatitis C and HIV are no longer contraindications
    - Diseases that recur in transplant:
        - IgA nephropathy (Berger's disease)
        - Goodpasture's syndrome (anti-GBM antibodies)
        - Diabetic nephropathy
        - Focal segmental glomerulosclerosis
        - Membranous glomerulonephritis
        - Membranoproliferative glomerulonephritis
        - Amyloidosis
        - Cystinosis

Diseases that do NOT recur in transplants

Polycystic kidney disease, primary hyperoxaluria (requires liver and kidney transplant)

-
    - Noncompliance
    - Psychiatric illness
    - Severe comorbidities
- **ABO typing**
- **Panel Reactive Antibody (PRA) Analysis**: recipient's serum tested for antibodies to multiple HLA subtypes
    - Presented as percentage of reactivity, so ***0% is good and 100% is bad.***
- **HLA crossmatch**
    - ***You want a NEGATIVE HLA crossmatch!!! (Positive is bad)***
- ***CT scan*** preoperative - evaluate renal vascular anatomy

Optimal Screening Results

ABO: identical to donor

HLA Crossmatch: negative

PRA Analysis: 0%

CANCER-FREE WAITING PERIOD FOR TRANSPLANT

- ***Kidney***
    - o Incidental, small (< 4 cm) = no wait; simultaneous partial / radical nephrectomy with transplant
    - o Large RCC or Wilm's tumor = 2 year wait after definitive treatment without recurrence
- ***Bladder***
    - o Carcinoma in situ (CIS) = no waiting
        - * Transplant patients are immunosuppressed, so BCG may not be an option
    - o Muscle invasive bladder cancer = 2 year wait after definitive treatment without recurrence
- ***Testicular / Prostate*** = 2 year wait after definitive treatment without recurrence
- ***Breast / Melanoma / Invasive cervical cancer*** = 5 year wait after definitive treatment without recurrence

LIVING DONORS

- Exclusion Criteria to Donate: < 18 or > 65 years old; HTN; diabetes mellitus; proteinuria; GFR < 80; polycystic kidney disease; hematuria; recurrent nephrolithiasis; clotting disorder; severe comorbidities; psychiatric issues
- ***Best kidney stays with the donor*** - transplant the kidney that has an anomaly
- If female / child bearing age, consider using the right kidney (left is normally transplanted due to longer renal vein) for transplant because of right-sided hydronephrosis during pregnancy

- Living donors have increased patient and graft survival, and decreased incidence of delayed graft function
- ***Donor urine output*** is the most important predictor of immediate graft function in living donor renal transplant

Renal Donor

Left kidney is preferred; however, best kidney stays with the donor

CADAVERIC DONOR CRITERIA

- Brain death donors
- Expanded cadaveric donors:
  - Age > 60
  - Age 50 - 60 with at least 2 of the following: CVA, HTN, Renal failure (Cr > 1.5)
  - 70% greater risk of graft loss than standard donor criteria

| SURGERY |

PRE-TRANSPLANT RECIPIENT NEPHRECTOMY

- Indications:
  - Hypertension not controlled by dialysis or medication
  - Persistent renal infection
  - Renal calculi or renal obstruction
  - Severe proteinuria
  - Polycystic kidneys - symptomatic from infection
  - Severe bleeding
  - Massive renal enlargement

- ***Renal embolization*** may only be performed on ***severe proteinuria*** from list above because the patient will likely continue to have issues without a nephrectomy.

TRANSPLANT - THE OPERATION

- Extraperitoneal transplantation approach since 1954
- One year graft survival is near 90%
- Usually the ***left donor kidney*** is placed in the ***right iliac fossa*** and vice versa
- Kidney is "flipped" - ureter anterior, vein posterior
- **Transplant locations**

1. Right iliac fossa
2. Left iliac fossa
3. High right iliac fossa
   - Note: If simultaneous or future pancreatic transplant, then place the kidney in the left iliac fossa, because the pancreas goes in the right iliac fossa.

- If an adult kidney is transplanted into a child: anastomose renal vein to IVC and renal artery to aorta
- If the renal vessels do not have enough length for a tension-free anastomosis, utilize the cadaveric iliac vessels to elongate the vessels
- Ureteroneocystostomy with double J stent placement
  - If duplicated ureteral system, may be implanted together (Wallace) or separately (Bricker)
  - If the ureter does not reach or is on tension, utilize routine techniques to reach the ureter or reduce tension (e.g. psoas hitch, Boari flap, etc.)
  - Ureteroureterostomy is an option, but rarely utilized

INTERNAL VS. EXTERNAL ILIAC ARTERY ANASTOMOSIS

- End-to-side anastomosis to the ***external iliac artery*** has been the preferred technique in ***deceased donors***, because of the large ***Carrel patch*** obtained from the aorta
  - Concern for early obstruction, late stenosis, and the steal phenomenon with ambulation.

- ***Classical kidney transplantation*** surgery (many still use currently, especially in living donors) was described using end-to-side anastomosis to the external iliac vein and end-to-end anastomosis to the ***internal iliac artery***.
    - Concern for erectile dysfunction and renal artery stenosis
- Men who have already had renal transplantation should have external iliac anastomosis for subsequent transplants in order to reduce the risk of erectile dysfunction.
- A randomized study of 38 ESRD patients with 3-year follow-up showed no difference between internal vs. external iliac artery anastomosis.

ESSENTIALS

- ***Limit cold ischemia time*** to decrease delayed graft function
    - Limit cold ischemia ideally to < 24 hours
    - May use pulsatile perfusion pump device for 48+ hours
- Small upper pole artery may be sacrificed
- ***Lower polar artery should be preserved*** to prevent ureteral ischemia and subsequent stricture
- Make sure the patient is adequately perfused; may give Mannitol to increase urine output immediately after transplant
- Once removed, rapid cooling by flushing blood from the kidney (very important)

| COMPLICATIONS |

- ***Urine leak / extravasation***
    - Dx: increased wound or drain output; fluid will have elevated creatinine level compared to serum creatinine
    - Tx: usually early revision is best approach, as a ureteral stent tends to delay the inevitable need for a revision
- ***Ureteral stricture***
    - If ureteral stricture < 2cm, endoscopic management
    - If ureteral stricture > 2cm, surgical repair

- ***Lymphocele***
  - Occurs in up to 35% of transplants
  - May present as DVT (iliac compression) or hydronephrosis (extrinsic ureteral compression)
  - Dx: abdominal ultrasound, CT scan
  - Tx: prevention with good surgical technique is key (minimize pelvic dissection, ligate lymphatics (versus cautery), postoperative drain)
    - Avoid sirolimus in early postoperative period when possible
    - If small / asymptomatic: observation
    - If large / symptomatic: percutaneous drainage, sclerosis, or peritoneal window
- ***Renal artery stenosis***
  - Many etiologies; occurs in up to 10% of transplants
  - Usually occurs within 3 years of transplant
  - If an ACE-inhibitor is given, the creatinine will acutely rise
  - Tx: if early diagnosis (1st few months): open revision
    - If later diagnosis: percutaneous transluminal angioplasty (PTA)
      - If unsuccessful: proceed to open revision
- ***Arteriovenous fistula***
  - Usually occurs after a renal biopsy
  - Majority are small and heal spontaneously
  - Tx: manage the same as non-transplant patients
- ***Ischemia-Reperfusion Injury***
  - Local inflammation which can lead to rejection
  - Exacerbates other complications and risk of transplant rejection
  - Tx: ***adequate hydration***, furosemide, mannitol
- ***Life-threatening immunosuppressant complications***
  - Etiology: cancer, coronary artery disease, severe sepsis, etc.
  - Tx: stop immunosuppressants and dialyze

DELAYED GRAFT FUNCTION

- ***Requirement for dialysis in first 7 days post-transplant***; occurs in up to 20% of deceased donor allografts
- 1% living allografts and 2% deceased allografts never function
- If initial and persistent oliguria = immediate renal Doppler flow for possible immediate re-exploration.
- Pre-renal etiologies
    - Vascular leak, thrombosis or stenosis
        - Renal artery / vein thrombosis: if identified in 1st few days, allograft preservation is possible; however, if late identification, will likely need allograft nephrectomy and another transplant
        - Dx: renal Doppler ultrasound or nuclear renal scan
    - Decreased intravascular volume, anemia, hemorrhage
        - Tx: intravenous fluids, blood transfusions prn
- Intrinsic etiologies
    - ***Acute tubular necrosis*** is most common cause overall
        - Dx: renal Doppler ultrasound and urinalysis
    - Renal parenchymal injuries
        - Nephrotoxic drugs (check drug levels as indicated)
        - Recurrence of original renal disease (see table at beginning of chapter for list of diseases that recur within the renal transplant)
        - Transplant rejection (see immunology section)
            - Dx: transplant biopsy
- Post-renal (obstruction) etiologies
    - Foley blockage
    - Blood clots
    - BPH: dry (little/no urine output) TURP has increased risk of vesical neck stricture and urethral stricture
    - Ureteral edema, "kinking", or stricture
    - Extrinsic ureteral compression
    - Sx: painless (transplant kidney is denervated)

- Dx: low urine output; increasing creatinine; increasing hydronephrosis; allograft enlargement
- Treatment
  - If early ureteral obstruction: consider revision
  - If late diagnosed ureteral obstruction: consider endoscopic ureteral stent placement, percutaneous nephrostomy, or revision

| IMMUNOLOGY |

- Banff 97 classification is a method for objective diagnosis of renal allograft pathology.

HYPERACUTE REJECTION

- Incompatible ABO or HLA = ***humoral***-mediated immunity
- ***Immediately to hours***
- Antibody mediated vascular thrombosis and necrosis
- Swollen, edematous organ
- Rare, due to current cross-matching and ABO-matching

ACCELERATED ACUTE REJECTION

- Possible anamnestic response mediated by antibodies and lymphocytes
- ***2-5 days after transplant***
- Oliguria; may have DIC, thrombocytopenia, hemolysis
- Arterial necrosis, vasculitis, lymphocyte infiltration
- Swollen, edematous kidney
- Intense ***CD4 deposition*** in the glomerular basement membrane
- Rare, no treatment

ACUTE REJECTION

- ***T-cell infiltration*** into the vascular and interstitial spaces; ***cellular*** rejection.
- ***Glomerulitis 7-10 days***, may recur during subsequent years
    - Takes a minimum of 1 week because it is mediated by T-cell differentiation, which ultimately damages the endothelial lining of the blood vessels
- 10% of transplants
- Diagnosis requires a transplant biopsy
- Tx: steroid pulse, antibody treatment
    - If antibody-mediated: add intravenous immunoglobulins (IVIg), plasmapheresis, anti-B-cell antibodies
- **Chronic Rejection**
- ***Glomerulopathy months to years*** after transplant
- Obliterative vasculopathy
- Essentially, occurs to all transplants to some degree
- No effective treatment; relentless deterioration

ANTIBODY MEDIATED REJECTION

- Etiology of acute and chronic allograft dysfunction and graft loss
- Renal biopsy for diagnosis
- Dx: ***CD4+ staining, DSA+ (donor specific antibodies)***; signs of acute or chronic injury

| IMMUNOTHERAPY |

- Goal of most immunotherapy agents is inhibiting stimulation, production, receptor binding and/or effects of IL-2 in its attempt to activate T-cells for rejection.

T-CELL ANTIBODY AGENTS

- ***OKT3, Anti-thymocyte globulin (Thymoglobulin®)***

- Cytotoxic antibodies to various T-cell antigens resulting in profound T-cell depletion
- Used for acute rejection prevention and treatment
- Side effects: myelosuppression, cytokine release syndrome (flu like symptoms)
    - Pre-medicate with corticosteroid, Tylenol, antihistamine: reduces side effects

CALCINEURIN INHIBITORS (CNI)

- Macrolide immunosuppressants: ***Cyclosporine (Neoral®, Gengraf®), Tacrolimus (Prograf®)***
- Prevents dephosphorylation of NFAT (nuclear factor of activated T-cells) by inhibiting calcineurin, thus preventing T-cell activation early on and ***inhibiting IL-2 production***
    - Normally calcium activates NFAT via calmodulin (calcium sensor protein), which activates calcineurin, thus allowing T-cell activation and IL-2 transcription
- Side effects: ***nephrotoxic***, HTN, reversible neurotoxicity
    - Nephrotoxicity is common
        - Biopsy: no inflammation = CNI toxicity
    - Cyclosporine – hirsutism, gingival hyperplasia, coarsening of facial features
    - Tacrolimus – diabetes, PTLD.

CORTICOSTEROIDS

- ***Methylprednisolone, Prednisone***
- ***Inhibits production of IL-2*** (T-cells), IL-1 (macrophage), and IL-6
- Blocks T-cell activation
- Side effects: obesity, glucose intolerance, adrenal cortical suppression, delayed wound healing, gastritis, osteoporosis, sodium/water retention, hyperlipidemia, HTN

ANTI-CD25 (T-CELL) MONOCLONAL ANTIBODY

- ***Daclizumab (Zenapax®), Basiliximab (Simulect®)***
- ***Anti-IL-2 receptor antagonists***: binds IL-2 receptor surface of T-cells, thus preventing IL-2 from activating the T-cells
- Administered during the 1st few weeks post-transplant as a rejection prophylaxis

MTOR RECEPTOR INHIBITOR

- ***Sirolimus (Rapamycin®)***
- Inhibits mTOR (mammalian target of Rapamycin) which ***blocks IL-2 stimulation of the cell cycle*** resulting in a lack of activation of T-cells and B-cells
    - NOTE: tacrolimus (CNI) inhibits the production of IL-2
- Lower nephrotoxicity than CNI's
- Side effects: myelosuppression, hyperlipidemia, wound complications, interstitial pneumonitis

ANTIMETABOLITES

- ***Mycophenolate mofetil (CellCept®, Myfortic®),*** Azathioprine (Imuran)
- ***Inhibits inosine monophosphate dehydrogenase*** (IMPDH) in purine biosynthesis (cell cycle) which is required for lymphocytic proliferation and activation
- Side effects: myelosuppression, diarrhea

ANTI-CD20 MONOCLONAL ANTIBODIES

- ***Rituximab (Rituxan®)***
- Interferes with ***B-cells*** by binding the antigen binding site for CD-20 protein
- Side effects: tumor lysis syndrome, cardiac arrest, infections, pulmonary toxicity

Common Renal Transplant Maintenance Regimen

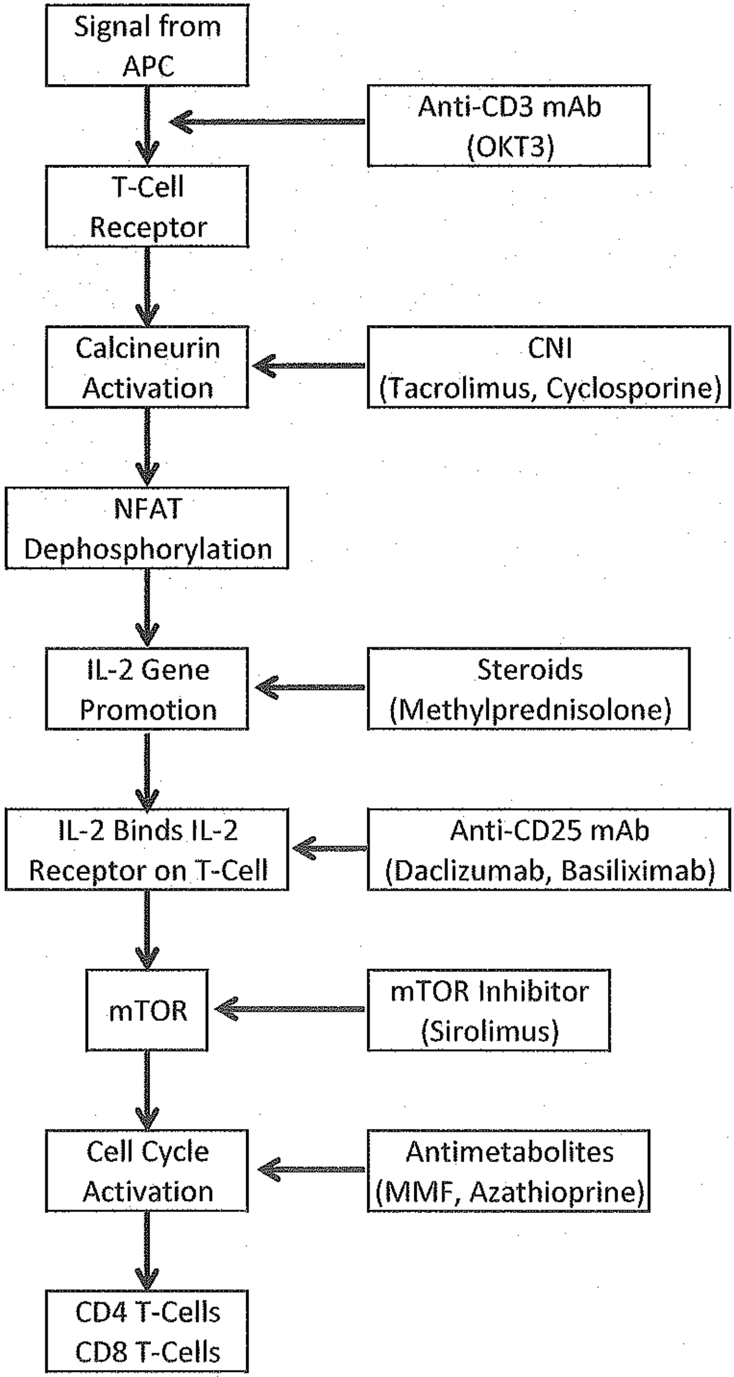
(1) CNI (Tacrolimus)

(2) Corticosteroids

(3) Antimetabolites (Mycophenolate mofetil) or

mTOR inhibitor (Sirolimus)

IMMUNE SYSTEM ACTIVATION AND IMMUNOSUPPRESSANTS


Signal from APC
Anti-CD3 mAb (OKT3)
T-Cell Receptor
Calcineurin Activation
CNI (Tacrolimus, Cyclosporine)
NFAT Dephosphorylation
IL-2 Gene Promotion
Steroids (Methylprednisolone)
IL-2 Binds IL-2 Receptor on T-Cell
Anti-CD25 mAb (Daclizumab, Basiliximab)
mTOR
mTOR Inhibitor (Sirolimus)
Cell Cycle Activation
Antimetabolites (MMF, Azathioprine)
CD4 T-Cells CD8 T-Cells

APC = antigen presenting cells; CNI = calcineurin inhibitor; IL-2 = Interleukin 2; mAb = monoclonal antibody; MMF = Mycophenolate mofetil; NFAT = nuclear factor of activated T-cells

| MALIGNANCY AND INFECTION |

POST-TRANSPLANT MALIGNANCY

- Increased risk of malignancy secondary to chronic immunosuppression
  - ***20% of renal transplant patients will have a malignancy at 10 years***
- Most common: ***squamous cell carcinoma*** (skin cancer) and ***post-transplant lymphoproliferative disorder***
  - Others Kaposi's sarcoma, non-Hodgkin's lymphoma
- Approximately 1 in 13 post-renal transplant deaths are due to malignancy
- ***Post-transplant Lymphoproliferative Disorder (PTLD)***
  - Majority occur within one year of transplant (relative risk 1-2%)
  - Likely related to ***Epstein-Barr Virus*** that results in ***uncontrolled B cell proliferation*** (non-Hodgkin's lymphoma)
  - Increased risk with Tacrolimus (CNI)
  - Tx: (1) ***withdraw/decrease immunosuppression*** (2) Ganciclovir (3) Rituximab (anti CD-20) and CHOP [Cyclophosphamide, Hydroxydaunorubicin (doxorubicin), Oncovin® (vincristine), and Prednisone] (4) nephrectomy

INFECTIONS

- ***Cytomegalovirus (CMV)***
  - "42-day fever" - occurs approximately 6 weeks after transplant.
  - Prophylaxis: antiviral (Ganciclovir)
- ***BK virus***
  - Non-enveloped double-stranded DNA Papovaviridae
  - Up to 30% will acquire virus, which may lead to BK nephropathy
  - Tx: cidofovir, fluoroquinolones are being investigated for prophylaxis

| ROUTINE MANAGEMENT |

- CIC is safe and effective in transplant patients!
- ***Erectile dysfunction***
    - Etiology: coronary artery disease; vascular disease; drug induced; decreased penile blood flow (if internal iliac-renal artery anastomosis, may lead to steal syndrome)
    - Phosphodiesterase type 5 inhibitors may be used in transplant patients; however, will likely need penile prosthesis (especially if steal syndrome)
- ESWL, PCNL, ureteroscopy with holmium laser are safe in a transplanted kidney

CHAPTER 34: SURGERY

| LAPAROSCOPY |

ABDOMINAL ENTRY

- Prior to entry, all laparoscopic procedures require a Foley catheter and orogastric or nasogastric tube (decompress the bladder and stomach)
- Open-entry (Hasson technique) vs. closed-entry (Veress needle, direct-trocar entry)
    - Neither technique is superior to reduce vascular/bowel injuries
    - Vascular injury: ~ 1/1000
    - Bowel injury: ~ 2/1000
    - Closed-entry has increased access failure
- ***Veress needle***: 2 resistance points upon entry: abdominal wall fascia and peritoneum
    - **Aspiration**: immediately upon needle entry to assure not within vascular or visceral organ
    - **Water drop test**: inject ~ 3cc of sterile saline, disconnect the syringe, and the saline within the needle hub should drain quickly into the peritoneal cavity
    - **Advancement test**: the needle should be able to be advanced ~ 1 cm without any resistance if within the peritoneal cavity
    - It is not advisable to lift the abdominal wall during entry; in fact it may decrease entry success

- ***Umbilical entry***: possible vascular injury (***right common iliac artery*** is the most common; aorta; vena cava)
    - Low BMI: enter at ~ 45° angle toward the pelvis to avoid aorta
    - High BMI: enter perpendicular to the abdominal wall to avoid entry failure
- ***Palmer's Point***: left upper quadrant Veress needle insertion
    - Be aware of ***superior epigastric vessels***
        - At the xiphoid process: ~ 4cm from midline
        - Halfway between xiphoid process and umbilicus: ~ 5.5cm from midline

Veress Needle Injury

If needle enters the bladder or bowel, simply remove the needle

- Radial expanding access system trocar entry has less bleeding than standard trocar
- ***Laparoendoscopic Single-Site Surgery (LESS)***
    - Single, small incision (≥ 2.5cm) may offer better cosmesis; however, more difficult to perform surgical procedure

PNEUMOPERITONEUM

- ***Carbon Dioxide (CO2) insufflant*** is most commonly used for pneumoperitoneum – high blood solubility and non-combustible
    - Hypercarbia (CO2 absorption)
- ***Helium*** may be used in patients with severe chronic respiratory disease to avoid hypercarbia
    - Less soluble in blood than CO2 (higher risk of embolism)
    - Insert ports with CO2, then switch to helium
- **Pneumoperitoneum** pressure ≤ 15 mmHg (10-12mmHg may be optimal)

  - ***Increases cardiac contractility, vascular resistance*** (i.e. **cardiac afterload**), and ***mean arterial pressure*** via sympathetic nervous system stimulation
  - ***Bradycardia*** is the most common cardiac arrhythmia associated with initiation of pneumoperitoneum
    - ***Tachycardia*** may ultimately develop secondary to sympathetic nervous system stimulation
  - ***Venous return*** (i.e. ***cardiac preload***) may be reduced from the compressive effects of pneumoperitoneum on the inferior vena cava
  - Higher pressures result in: acidosis, decreased GFR, worse oliguria (≤ 10mmHg pressure and furosemide improves urine output), decreased venous return (if euvolemic or hypovolemic), increase systemic vascular resistance, may decrease mesenteric blood flow

- ***Carbon dioxide (gas) embolism***: usually occurs during Veress needle entry via injury and insufflation of an organ or vessel
  - Embolism obstructs the right ventricle and pulmonary artery, and may cause a gas lock and ultimately, cardiovascular collapse/death
  - Increased pulmonary artery pressure → ***hypotension, tachycardia***
  - ***Mill-wheel murmur*** may be present
  - Transesophageal echocardiogram may be used to diagnose
  - Tx: deinsufflate the abdomen; 100% oxygen via endotracheal tube (CO2 washout); place the patient in ***Trendelenburg combined with left lateral decubitus position*** (***Durant's maneuver***; allows gas embolism to rise to the anterior right atrium); insert a central line into the right ventricle/atrium and aspirate the CO2
    - If cerebral CO2 embolism, consider hyperbaric oxygen therapy

- ***Pleural injury (Pneumothorax)***: if incidental injury to the diaphragm / pleura and the patient is stable, place a catheter or nasogastric tube laparoscopically in the pleural cavity. Place a purse-string suture in the diaphragm around the tube. Give a positive pressure breath, suction the tube to evacuate the pneumothorax, and then simultaneously tighten the suture while removing the tube.
    - A chest tube is usually not necessary if the patient is stable
    - May fill the respective upper quadrant with water to assess for air leak, and need for further repair
    - Postoperative chest x-ray is imperative

ABDOMINAL EXIT

- ***Residual CO2*** insufflant is irritative to the diaphragm, which will cause referred pain to the shoulder via the ***phrenic nerve***
    - Upon removing the ports, anesthesia should give several large positive pressure breaths to help evacuate remaining CO2
- ***Port site hernia***
    - Entry site closure should be considered for ≥ 10mm ports; in children consider closing all ports ≥ 5mm
    - Port site hernias 1-3% (larger ports have a higher risk of hernia)
- ***Port site bleeding***
    - Check all port sites upon exiting the abdomen. Figure-of-eight suture or pinpoint cautery any port site that is bleeding.

| INGUINAL HERNIA |

ANATOMY

- ***Inguinal (Poupart's) ligament***: formed from the external abdominal oblique muscle, and runs from the anterior superior iliac spine to the pubic tubercle
- ***Lacunar (Gimbernat's) ligament***: formed from the external abdominal oblique muscle, and is splayed between the inguinal and pectineal ligaments near the pubic tubercle

- ***Pectineal (Cooper's) ligament***: extension of the lacunar ligament and thickening of the pectineal line fascia; it runs along the superior pubic ramus
- ***Hesselbach's Triangle***: triangle formed by the rectus abdominis muscle, inguinal ligament, and inferior epigastric vessels
  - o ***Direct hernia***: hernia ***medial*** to the epigastric vessels through inguinal canal floor in Hesselbach's Triangle
    - * Inguinal canal floor: transversalis muscle
  - o ***Indirect hernia***: hernia ***lateral*** to the epigastric vessels through the internal inguinal ring
    - * Secondary to ***patent processus vaginalis***
    - * Associated with ***hydrocele***
  - o ***Pantaloon hernia***: direct and indirect hernia
- ***Reducible hernia***: ability to push the hernia contents back into the abdomen
- ***Incarcerated hernia***: inability to reduce the hernia
- ***Strangulated hernia***: incarcerated hernia that is resulting in ischemia to the hernia contents (e.g. bowel)

Gender and Hernias

Inguinal hernias are most common in both genders, but in regards to femoral hernias, they occur more commonly in females

HERNIA REPAIRS

- ***Lichtenstein***: tension-free onlay mesh repair between the conjoined tendon and inguinal ligament with anchoring to the pubic tubercle
- ***Bassini***: suture approximation of the conjoined tendon to the inguinal ligament
- ***McVay***: suture approximation of the conjoined tendon to the Cooper's ligament
- ***Shouldice***: four layer reconstruction

- ***Laparoscopic***: indicated for bilateral hernias, recurrent hernias, or necessity to have quick return to activity (e.g. athletes)

| MISCELLANEOUS |

NEEDLE STICK / VIRAL EXPOSURE

- ***Hepatitis B virus (HBV)*** is the most contagious virus (up to ~1/3)
  - o Postexposure prophylaxis (PEP): HBV vaccination (if unvaccinated); hepatitis B immunoglobulin
  - o Acute → chronic hepatitis B (5-10%)
  - o Chronic hepatitis B → cirrhosis/liver carcinoma → death (~ 25%)
- ***Hepatitis C virus (HCV)***: no immediate PEP; monitor for seroconversion long term
- ***HIV*** seroconversion is rare (0.4%)
  - o Immediate PEP upon HIV exposure; continue for 4 weeks if the patient is found to be HIV positive
  - o Negative rapid-HIV test may eliminate the need for prophylaxis

PATIENT POSITIONING INJURIES

- Supine: ***ulnar nerve*** injury is most common in this position (results in ***claw hand***)
  - o Related to hyperextension of the elbow (increased flexion may also resulting in stretching of the ulnar nerve)
  - o ***Brachial plexus*** injury: adduction of the arm > 90° or external rotation
- Hyperextended supine: spinal cord ischemia/infarct from stretch placed on the spinal cord (never hyperextend > 10° to avoid)
- Trendelenburg: facial/laryngeal edema; ischemic optic neuropathy
  - o Robotic surgery may utilize steep Trendelenburg, which may exacerbate these complications
- Prone: ***Brachial plexus*** injury (avoid with arm extension < 90°, elbows flexed, palms down); ischemic optic neuropathy

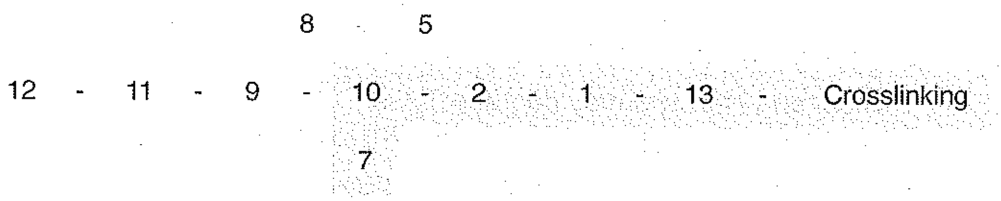
  - Avoid cervical hyperextension
  - Chest rolls bilateral to avoid breast compression in females
- Lateral recumbent: requires axillary roll to avoid ***brachial plexus*** injury
  - Bottom leg bent, top leg straight
  - Lateral position has increased risk of rhabdomyolysis and skin breakdown
- Lithotomy: ***common peroneal nerve*** injury is most common in this position (results in ***foot drop***) – avoid compression of lateral calf/knee in stirrups
  - Lowering of the legs may result in hypotension secondary to redistribution of venous blood volume

Lithotomy Positioning

Peroneal nerve is the most common nerve injury from prolonged lithotomy. Patient presents with foot drop postoperatively

| HEMOSTATIC PRODUCTS |

COAGULATION CASCADE



- ***Intrinsic pathway***: starts with factor 12; activated by intravascular insult
- ***Extrinsic pathway***: starts with factor 7 and tissue factor; activated by extravascular insult
  - Shaded area on cascade above

- **Factor 2** = prothrombin
- **Factor2a** = thrombin
- **Factor 1** = fibrinogen
- **Factor 1a** = fibrin

THROMBIN-BASED HEMOSTASIS

- **Floseal®** - human thrombin + gelatin matrix + calcium chloride
    - Indication: adjunct to hemostasis
    - Once reconstituted, may be used over the next 2 hours
    - Do not leave in renal collecting system / ureter as it may become a nidus for calculi
- **Thrombin JMI®** - bovine prothrombin + bovine tissue thromboplastin + calcium chloride
    - Indication: adjunct to hemostasis of small venules or capillaries
    - May be used with absorbable gelatin sponge
    - May develop bovine antibodies that cross react with factor 5, resulting in factor 5 deficiency

FIBRIN-BASED HEMOSTASIS (NOTE: DOES CONTAIN THROMBIN)

- **Tisseel®** - thrombin + sealer protein solution (including fibrinogen, aprotinin) + calcium chloride
- Indications: adjunct to hemostasis; prevent leakage from colonic re-anastomosis
- Once thawed, will last 48 hours if unopened
- Once reconstituted, may be used over next 4 hours
- Alcohol and betadine may degrade Tisseel

MISCELLANEOUS

- **Gelfoam®** - porcine gelatin
- **Surgicel®** - oxidized cellulose
- **Avitine®** - microfibrillar collagen powder
- **Arista®** - absorbable microporous polysaccharide particles (plant starch)

- **Cyanoacrylate** – medical skin glue
  - Octyl cyanoacrylate: weaker bond, but more flexible
  - n-Butyl cyanoacrylate: stronger bond, but more rigid

| LASERS |

- ***Lasers*** = Light Amplification by the Stimulated Emission of Radiation
  - Pulse vs. continuous: pulse mode is more precise
  - Wavelength: determines penetration depth; molecule absorption (e.g. water, hemoglobin)
  - Energy: strength of the laser transmitted
- ***Carbon Dioxide***
  - 10,600 nm light wave
  - Heavily absorbed by water…limited tissue penetration
  - Penetrates < 0.1 mm (thermal effect 0.5 mm)
  - Uses: skin lesions (e.g. HPV), superficial penile cancer
- ***Holmium:YAG (YAG = Yttrium Aluminum Garnet)***
  - 2,100 nm light wave
  - Strongly absorbed by water
  - Thermal injury is 0.5-1mm
  - Uses: lithotripsy, incisions (e.g. UPJO, stricture, bladder neck contractures, posterior urethral valves), HoLEP/HoLAP
- ***Nd:YAG (Nd = neodymium-doped)***
  - 1,064 nm light wave
  - Penetrates 5-7 mm
  - Uses: BPH (coagulation effect); decreased bleeding secondary to a high affinity for hemoglobin
- ***KTP (potassium-titanyl phosphate)***
  - 532 nm light wave
  - Nd:YAG laser that goes through a KTP crystal, which ultimately halves the wavelength and doubles the frequency; results in decreased penetration of tissue

  - Uses: Incisions (e.g. urethral strictures, bladder neck contractures), BPH (vaporization), bladder cancer (small, low grade Ta disease), urethral lesions
- ***Nitrogen Laser***
  - 337 nm light wave
  - Uses: autofluorescence (identification of bladder tumors)
- ***Tissue Coagulation vs. Vaporization***
  - Coagulation: < 100°C → denatured proteins → coagulation → tissue sloughing
  - Vaporization: 100-300°C instantaneous tissue vaporization / debulking

CHAPTER 35: SYNDROMES

This is a rapid review of syndromes that impact the genitourinary system. See respective chapters for further details on selected syndromes. Many of these syndromes may appear as "distractor" answer choices.

PRUNE BELLY SYNDROME (EAGLE-BARRETT OR TRIAD SYNDROME)

- Cryptorchidism
- Abdominal wall musculature defect
- Urinary tract anomalies (e.g. renal dysplasia, hydroureter, dilated prostatic urethra)

WAGR SYNDROME

- Defect on WT1 gene (11p13)
- **W**ilms' tumor
- **A**niridia
- **G**enitourinary abnormalities (hypospadias/UDT)
- **R**etardation (mental)

BECKWITH-WIEDEMANN SYNDROME

- Congenital defect on WT2 gene (11p15) resulting in overgrowth disorder
- Macrosomia, macroglossia, hemihyperplasia, omphalocele, visceromegaly, hypoglycemia
- Increased risk of Wilms tumor, rhabdomyosarcoma, hepatoblastoma
- Approximately 10-15% have medullary sponge kidney

VACTERL

- Constellation of abnormalities of the mesoderm
- **V**ertebral defects
- **A**nal atresia
- **C**ardiac defect (ventricular or atrial septal defects, tetralogy of Fallot)
- **T**racheo-**E**sophageal fistula
- **R**enal defects (e.g. horseshoe kidney, agenesis, hypoplasia)
- **L**imb defects

KLINEFELTER SYNDROME

- 47, XXY
- Primary testicular failure with seminiferous tubule degeneration
- Tall, eunuchoid body habitus, atrophic testicles, azoospermia, breast cancer, cognitive disability
- Hypergonadotropic hypogonadism (high FSH/LH, low Testosterone)

TURNER SYNDROME

- 45, XO
- Premature ovarian failure with streak ovaries
- Lack secondary sexual characteristics, primary amenorrhea, horseshoe kidney, aortic coarctation, webbed neck
- Hypergonadotropic hypogonadism (high FSH/LH, low estrogen)

NOONAN'S SYNDROME (*"MALE TURNER SYNDROME"*)

- Somatic chromosome defect
- Male = Female incidence
- Webbed neck, short stature, shield chest, cognitive disability, hypertelorism, down slanting eyes, congenital heart disease
- Normal FSH/LH, testosterone, estrogen

SWYER SYNDROME

- 46, XY with complete gonadal dysgenesis lacking testosterone and mullerian inhibiting substance

- Genetically a male; phenotypically a female
- High risk for gonadoblastoma → bilateral gonadectomy

DENYS-DRASH

- Defect on WT1 gene (11p13)
- Wilms' tumor
- DSD (gonadal dysgenesis)
- Nephropathy (diffuse mesangial sclerosis)

MAYER-ROKITANSKY-KUSTER-HAUSER (MRKH) SYNDROME

- 46, XX with a defect in WNT4 gene (1p36) resulting in absent Mullerian (paramesonephric) ducts
- Normal external female genitalia and absent uterus and fallopian tubes
- Presents with primary amenorrhea
- Associated with renal anomalies

TUBEROUS SCLEROSIS

- Autosomal dominant defect on 9q34 (TSC1); 16p13 (TSC2)
- Sebaceous adenoma, seizures, mental retardation, angiomyolipoma
- Slight increased risk of renal cell carcinoma

WUNDERLICH SYNDROME

- Massive retroperitoneal hemorrhage associated with angiomyolipoma

VON HIPPEL-LINDAU (VHL) DISEASE

- Tumor suppressor gene of VHL gene at 3p25-26
- Renal cell carcinoma – clear cell type, pheochromocytoma, retinal angiomas, hemangioblastomas

STAUFFER SYNDROME

- Renal cell carcinoma paraneoplastic syndrome resulting in abnormal liver function tests without evidence of liver metastasis or involvement
- Majority resolve with nephrectomy

BIRT-HOGG-DUBE SYNDROME

- Mutation of folliculin gene on chromosome 17p11
- Renal cell carcinoma – chromophobe type and/or oncocytoma, cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax

SHY DRAGER SYNDROME

- Multiple systems atrophy = Parkinsonism + autonomic dysfunction
- Bladder overactivity, poor compliance, open bladder neck, external urethral sphincter denervation

CONN'S SYNDROME (PRIMARY HYPERALDOSTERONISM)

- Benign, adrenal, aldosterone-secreting adenoma
- Hypokalemia, alkalosis
- Serum potassium (< 3) and aldosterone to plasma renin activity ratio (> 20:1)

CUSHING'S SYNDROME

- ***Cushing's Syndrome***: excessive cortisol with symptoms from any cause
- ***Cushing's Disease***: excessive cortisol with symptoms from increased anterior pituitary secreted ACTH

ADDISON'S DISEASE

- Primary adrenocortical insufficiency (glucocorticoid and mineralocorticoid deficiency)
- Elevated ACTH (hyperpigmentation), progressive weakness, hypotension unresponsive to fluid challenge, nausea, vomiting, pseudo-acute abdomen
- Tx: hydrocortisone ± fludrocortisone

MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES

- ***MEN 1 (Wermer Syndrome):*** pituitary adenoma, parathyroid hyperplasia, pancreatic tumor
- ***MEN 2a (Sipple Syndrome)***: Pheochromocytoma, medullary Thyroid Carcinoma, parathyroid hyperplasia / adenoma
- ***MEN 2B:*** Pheochromocytoma, medullary Thyroid Carcinoma, mucosal

and gastrointestinal neuroma, marfanoid features

  - MEN 2 syndromes also referred to as PTC syndrome (*p*heochromocytoma, *t*hyroid *c*arcinoma)

NELSON'S SYNDROME

- Pituitary adenoma after bilateral adrenalectomy
- Elevated ACTH (lacks negative feedback)
- Hyperpigmentation, headaches, visual changes

WATERHOUSE-FRIDERICHSEN SYNDROME

- Hemorrhagic adrenalitis; most commonly caused by Neisseria meningitidis

SHEEHAN'S SYNDROME

- Post-partum hypopituitarism secondary to necrosis / hypoperfusion

REITER SYNDROME

- Autoimmune response to non-gonococcal urethritis
- Conjunctivitis and arthritis ("Can't pee, see, or climb a tree")
- ***Balanitis circinata***
- Associated with HLA-B27
- Tx: doxycycline

BEHCET'S SYNDROME

- Immune-mediated vasculitis
- Aphthous ulcers, genital ulcers and uveitis
  - Do not confuse with Herpes
- Tx: corticosteroids and immunosuppressants

HINMAN'S SYNDROME

- Non-neurogenic neurogenic bladder
- Learned, voluntary detrusor sphincter dyssynergia, which may result in bladder outlet obstruction symptoms (e.g. urinary retention, bladder trabeculation, hydronephrosis)
- Tx: anticholinergics, timed voiding, biofeedback, bowel regimen

ELSBERG SYNDROME

- Acute urinary retention from Herpes Simplex Virus type 2, sacral radiculomyelitis
- Motor dysfunction
- Tx: self-limited (< 12 weeks), timed voiding and CIC prn

FOWLER'S SYNDROME

- Young woman with urinary retention from an inability to relax the external sphincter in the absence of neurologic disease
- Associated with polycystic ovarian syndrome
- Tx: sacral nerve stimulation, CIC

MENKES' SYNDROME (KINKY HAIR SYNDROME)

- Copper metabolism disorder (copper deficiency)
- Children with multiple bladder diverticula, urinary retention, coarse hair, hypotonia

EHLERS-DANLOS SYNDROME

- Congenital collagen metabolism disorder
- Skin and joint laxity, hypotonia, recurrent hernias, bladder diverticulum

GOUVERNEUR'S SYNDROME

- Classic presentation of vesicoenteric fistula
    - Suprapubic pain, urinary frequency, dysuria, tenesmus
- Pneumaturia, fecaluria, recurrent UTI may also be present

KALLMANN SYNDROME

- Congenital hypogonadotropic hypogonadism with anosmia
- Low FSH/LH, low testosterone

YOUNG'S SYNDROME

- Obstructive azoospermia, bronchiectasis, sinusitis
- Abnormally thick epididymal secretions
- Tx: IVF/ICSI

KARTAGENER SYNDROME (PRIMARY CILIARY DYSKINESIA)

- Autosomal recessive; situs inversus, chronic sinusitis, bronchiectasis
- Immotile sperm leads to infertility
- Tx: IVF/ICSI

LESCH-NYHAN SYNDROME

- X-linked recessive; hypoxanthine-guanine phosphoribosyltransferase deficiency
- Hyperuricemia, hyperuricosuria, uric acid calculi, self mutilation

LOIN PAIN-HEMATURIA SYNDROME (LPHS)

- Recurrent flank pain and micro- or macro- scopic hematuria
- Etiology is unknown; usually young women
- Tx: pain control, encourage fluids

LERICHE SYNDROME

- Atherosclerosis of the aorta and iliac arteries
- Triad: erectile dysfunction, buttock claudication, absent / diminished femoral pulses
- Tx: aortoiliac bypass

OVARIAN VEIN SYNDROME

- Ureter compression by a dilated ovarian vein, resulting in hydroureter
- Tx: ovarian vein embolization or ligation

METABOLIC SYNDROME

- Insulin resistance, diabetes mellitus type 2, hypertension, obesity, dyslipidemia

- Associated with benign prostatic hyperplasia, erectile dysfunction, hypogonadism, cardiac disease

HEPATORENAL SYNDROME

- Severe renal vasoconstriction resulting in acute renal failure with underlying decompensated cirrhosis / portal hypertension

- Tx: liver transplant, dialysis

ALPORT SYNDROME

- X-linked dominant; mutations in collagen type 4
- Glomerulonephritis, hematuria, sensorineural hearing loss, anterior lenticonus (vision deterioration)

HEMOLYTIC UREMIC SYNDROME (HUS)

- Microangiopathic hemolytic anemia, thrombocytopenia, renal failure
- Seen in pediatrics after ingestion of E. coli O157:H7

BERDON SYNDROME (MEGACYSTIS-MICROCOLON-INTESTINAL HYPOPERISTALSIS SYNDROME)

- Autosomal recessive; rare
- Constipation, urinary retention with a dilated bladder, intestinal hypoperistalsis with a small colon
- Majority die within 1 year

KLIPPEL-TRENAUNAY SYNDROME

- Soft tissue and bone overgrowth, varicose veins, port-wine stain, bladder hemangiomas
- Tx: if hematuria → cystoscopy with Nd:YAG laser ablation